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## American Gynecological Society

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*(Concluded)*

### HYDATIDIFORM MOLE—A PATHOLOGICO-CLINICAL CORRELATION OF 200 CASES\*†

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IT IS the purpose of this paper to determine what, if any, correlation there exists between the histologic appearance of a hydatidiform mole and the subsequent clinical course of the patient with respect to the development of chorionic malignancy. Because of the lack of any universally recognized histologic criteria, which invariably separate the malignant from the benign moles, it has been stated by some pathologists<sup>1, 10, 15, 16, 18, 21</sup> that such criteria do not exist. Other authors,<sup>14, 22</sup> however, state that such criteria do exist and can be correlated with the patient's clinical course.

In going over the literature from 1937 (when Mathieu<sup>11, 12</sup> reviewed it) up until the present time, it is evident that no systematic attempt has ever been made to correlate pathologically a series of moles with their clinical outcome. To accomplish this correlation it was decided in 1935, when one of us (A.T.H.) was Assistant Pathologist of the Boston Lying-in Hospital, to collect from various obstetric clinics, general hospitals, and other interested contributors, a large enough series to determine whether such a correlation exists. This study has gone on since that time, although the 200 cases in this report were collected from January, 1932, to January, 1942—a period of approximately eleven years.

#### Material and Methods

The source of this material is from 109 medical communities in the eastern half of the United States. To all of the many contributors, we are individually and collectively grateful, for without their help it would have been mani-

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festly impossible to carry out this study. To Dr. F. C. Irving we are indebted for encouragement and help in placing the series from the Boston Lying-in Hospital at our disposal. To Drs. S. B. Wolbach, Shields Warren, Olive Gates, and Frederick Parker, Jr., we are indebted for advice and diagnostic help. Misses Carmen Atwell and Ruth Daegy have materially assisted with this study by their secretarial help in keeping the records of these patients up to date. Dr. Florence C. Slater has aided greatly by helping to review the literature from 1942 to the present time.

In order to make this study as objective as possible, every case was studied independently by each of us. If a disagreement in the histologic grading of the mole was encountered, we rationalized our differences of opinion before either of us became aware of the patient's clinical course. Some of the cases, such as those from our own clinic, were sent to us for a pathologic opinion, so that in such instances the clinical outcome was not yet known. In reviewing old cases, on whom clinical data were available, the latter was not recorded on the master sheet for each case until our final diagnosis had been made. In the rare case whose identity one of us recognized, either by its particular histology, shape of the section, or pathologic number, it was fortunate that the other observer failed to recognize the identity of the specimen; and, hence, the objectivity of the grading was preserved. In some instances, we had both the molar tissue as well as uterine curettings. If the former showed a lower histologic grading than the latter, or vice versa, the grading of the mole became the final diagnosis. In this way the study became a more objective correlation between the mole per se and its clinical course. In actual practice, of course, the pathologist should and does make his final report on all the available evidence.

During the course of the study, it became evident that some histologic criteria had more significance with respect to malignancy than did others. We naturally used such information in grading subsequent moles. Also, in going back over previously graded moles, whose identity purposely remained anonymous, we applied these progressively learned criteria to the earlier cases so as to make all grading uniform. It seemed unfair to us, as well as unobjective, finally to misgrade an early mole in the series merely because of ignorance of the significance of a particular histologic pattern.

The question naturally arises as to whether such results from a series of 200 moles are statistically significant.\* The number of cases in this study was not chosen on the basis of statistical validity, although it was hoped to get as large and significant a series as possible. Since the average incidence of hydatidiform mole is one in approximately 2,000 deliveries (1:2,051 for the 14 Boston Lying-in cases from the Ward Service), these cases represent, on an average, the moles from 400,000 pregnancies, or about one-seventh of all the deliveries in the United States during 1945.

The question of whether these cases represent an adequate random sampling of moles throughout the country is also pertinent.\* The middle and northern Atlantic coastal regions are well represented, and a few specimens were obtained from portions of the middle western and southern states east of the Mississippi River. It appears from a review of the literature, in comparison with this series, that all of the major varieties and complications of hydatidiform mole are represented in this material; these include all the grades of ultimate malignancy with their usual prognosis, death from postoperative sepsis, spontaneous perforation of the uterus, and fatal hemorrhage following evacuation of the mole. One of our patients even had three successive hydatidiform moles, all benign. Hence, the data and conclusions appear not only medically sound, but statistically valid.

\*Miss Jane Worcester of the Department of Biostatistics, Harvard School of Public Health, has kindly gone over the data of this paper. The material represents an adequate random sample of hydatidiform moles. She feels, furthermore, that it is not necessary to subject the data to statistical analysis since the conclusions are obviously valid.

To be sure, some of these cases have been sent from other clinics as diagnostic problems, but they are in the minority. The vast majority of the outside cases were obtained by contacting persons who had access to such material so that the cases from any clinic, hospital, or locality tend to be a random sample from that region.

### Histologic Grading of Hydatidiform Moles

In grading these potentially malignant tumors, two general histopathologic principles were kept in mind: (1) the degree to which the trophoblast resembled or differed from that of normal placental tissue in the first trimester of pregnancy, and (2) the absolute degree to which it appeared to be undifferentiated, using the criteria employed in grading any tumor. Comparison with first trimester trophoblast was used as a criterion, since it is from pathologic chorions of this general developmental age that hydatidiform moles arise. (For details of the genesis of these structures see Hertig and Edmonds.<sup>4</sup> As the study progressed, it became clear that the more malignant the mole, the more its trophoblast resembled the differentiating trophoblast of the early human ovum during its first week after implantation. Histologic details of such early ova are found in the papers of Hertig and Rock,<sup>5, 6</sup> and Heuser, Rock, and Hertig.<sup>9</sup>

The usual morphologic criteria of malignancy, such as pleomorphism, degree of cellular differentiation, abnormal rate of growth, loss of basement membrane, invasion of stroma, and vascular invasion (universally observed by pathologists in grading all tumors) were also used. These principles were employed, since it was assumed that actual malignancies must follow the general rules of tumor growth, invasion, and metastasis. However, it is evident from a study of placental development and growth that a tumor derived from trophoblast differs from any other tumor in two fundamental respects: (1) it is derived from structures that are not an integral part of the host, and (2) its benign prototype is normally invasive, opens and permeates blood vessels, and thereby often metastasizes to the lungs.

Because of the first fundamental difference, namely, the tumor host relationship, it is theoretically possible (and actually quite probable) that no matter how malignant a mole appears microscopically, any particular area of trophoblast may not have been in juxtaposition to the uterine wall, and hence could not have invaded it. This probably explains the lack of any absolute clinico-pathologic correlation which plagues all pathologists who attempt to grade an individual hydatidiform mole. Furthermore, since a mole is often a bulky structure and has been shown to vary in microscopic appearance from portion to portion, it is imperative to select at least five, and preferably ten, regions for routine study. Particular attention should be paid to curettings, for they offer the best possibility of evaluating a mole. Too often the clinician has carefully saved the mole and borne it proudly to the pathologic laboratory, having discarded the curettings as being inconsequential to the diagnosis.

The second fundamental difference, namely, the semimalignant attributes of all trophoblast, makes it clear that, since most pregnant patients have trophoblastic metastases, but rarely die from chorionepithelioma, there must be some factor other than its pure morphologic appearance which allows one metastasis to persist and kill the patient, while the other disappears. The lytic substance postulated by Fraenkel<sup>3</sup> is possibly the explanation for this phenomenon.

With all these difficulties in mind, it is still possible to correlate in a general fashion the malignant potential of a hydatidiform mole with the clinical outcome of the patient. This becomes apparent in a large series, as shown in Table I, although not always so evident in any individual case. Fig. 1 is a

graphic representation of the percentage distribution of the various molar groups in the series. It is evident that the largest group (29.5 per cent) of the cases are classified as possibly malignant (Group IV), although only 17 per cent of this group showed ultimate malignancy of some degree or other (Fig. 2). This single fact emphasizes what all pathologists and clinicians have suspected, namely, that many moles may look fairly malignant, but few actually become so. Fig. 2 summarizes the distribution of the various grades of chorionic malignancies according to the molar group into which they were originally placed. Thus, for example, only 10 of the 59 possibly malignant moles (Group IV) actually realized their malignant potentiality, even though all looked more or less alike as original moles. It must be emphasized further that the various grades of chorionic malignancy vary widely in ultimate clinical prognosis, irrespective of their original molar grouping. This will be dis-

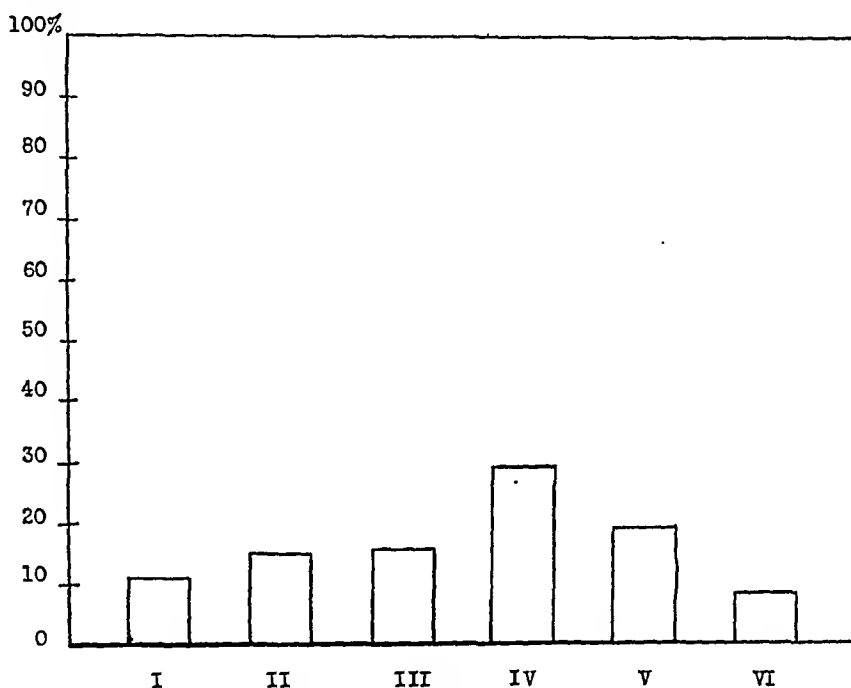


Fig. 1.—Distribution of molar groups in 200 cases of hydatidiform mole.

cussed more in detail later. Fig. 3 graphically represents the percentage distribution of the clinically malignant varieties of chorionepithelioma according to their original molar grouping. By comparing Figs. 2 and 3, it becomes apparent that there is still a correlation between the original grouping of a mole, irrespective of whether one includes all grades of chorionic malignancy (Fig. 2) or only the clinically malignant chorionadenoma destruens and chorioncarcinoma (Fig. 3). In spite of the lack of specific clinico-pathologic correlation in any given mole, the information gained from this study has enabled the authors to evaluate the malignant potentiality of an individual mole much more accurately than before the study was undertaken.

### I. Benign Hydatidiform Moles

(None to slight hyperplasia of trophoblast)

In this group there were 22 specimens, none of which showed either pathologic or clinical evidence of malignancy. Adequate follow-up data are available for this group, as summarized in Table III. The details of such prognostic data will be reserved for discussion later on in the paper.

None of these moles show a significant departure from the normal trophoblast pattern of immature chorionic villi. The villous stroma, as of all moles, has been converted into a cystic mass at the periphery of which is a layer of loose, avascular, fibroblastic, or mesoblastic tissue. The trophoblast of some villi still possesses a normal double-layered epithelium of the classic pattern. Many villi, however, show mechanical thinning and distortion of their epithelial covering, presumably due to stretching incident to hydropic swelling of the villus. In occasional areas of nearly every mole of this group is slight benign proliferation of syncytium and/or Langhans epithelium, as shown in

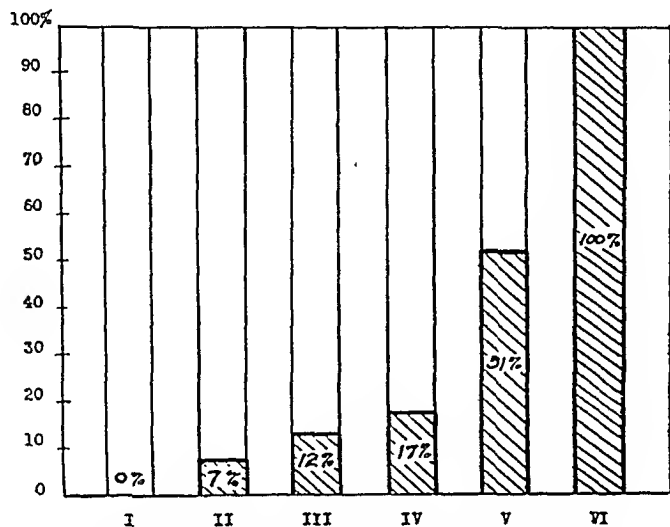


Fig. 2.—Distribution of all grades of chorionic malignancies by molar groups in 200 cases of hydatidiform mole.

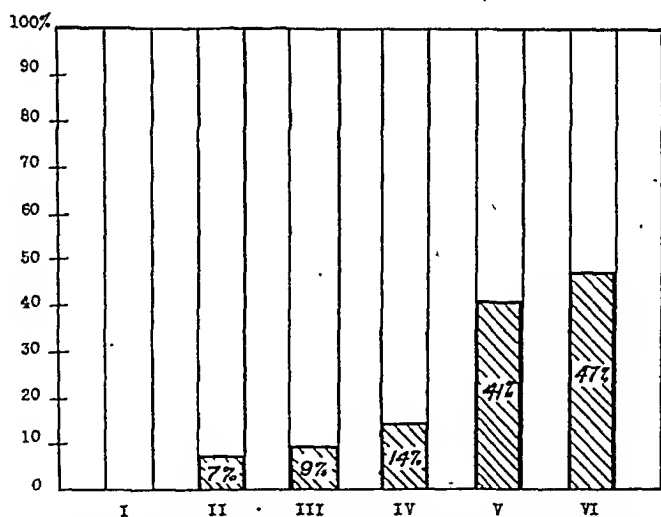


Fig. 3.—Distribution of chorionic malignancies by molar groups (including only chorionadenoma destruens and chorioncarcinoma) in 200 cases of hydatidiform mole.

Fig. 4,A. The relative proportion of these proliferative epithelial elements is by no means constant, either from field to field in the same mole or in the group as a whole. The Langhans epithelium and its associated trophoblastic masses, comparable to cell columns of the normal villi, are often the seat of "fibrinoid" degeneration. This is a normal occurrence in aging trophoblast, as pointed out by Wislocki and Bennett.<sup>23</sup> Mitoses in the Langhans epithelium are no more frequent, indeed appear less so, than in the normal immature villi of six to twelve weeks. Mitoses never occur in syncytium, in our experience, either in early ova, developing placentas, or hydatidiform moles.

TABLE I. HYDATIDIFORM MOLE CLASSIFICATION

GROUP	NAME	HISTOLOGIC CRITERIA	NO. CASES	NO. MALIG-NANCIES
I	Benign	None to slight hyperplasia of tropho-blast	22	0
II	Probable benign	Slight to moderate hyperplasia	30	2
III	Possible benign	Hyperplasia with slight anaplasia	33	4
IV	Possible malignant	Moderate anaplasia with hyperplasia	59	10
V	Probable malignant	Marked anaplasia with hyperplasia	39	20
VI	Malignant	Exuberant trophoblastic growth (variable mitotic activity) with marked anaplasia, and often evidence of endometrial invasion	17	17
Totals			200	53

TABLE II. GRADES OF 53 CHORIONIC MALIGNANCIES DISTRIBUTED ACCORDING TO MOLAR GROUPS IN 200 CASES OF HYDATIDIFORM MOLE

	I	II	III	IV	V	VI	TOTAL CASES	PER CENT
Chorionepithelioma in situ	0			1	1	5	7	3.5
Syncytial endometritis	0		1	1	3	4	9	4.5
Chorionadenoma destruens	0	2	3	8	13	6	32	16.0
Chorioncarcinoma	0				3	2	5	2.5
Total	0	2	4	10	20	17	53	26.5

TABLE III. FOLLOW-UP DATA ON CLINICALLY BENIGN MOLES

ORIG. GROUP	CASES	SUBSE-QUENT PREG-NANCY	ALIVE AND WELL TWO (+) YEARS	ALIVE AND WELL TWO (-) YEARS	NO DATA	REMARKS
I	22	12	5	5	0	
II	28	13	9	2*	4	*One with negative uterus on hysterectomy and one with negative curettings from uterus.
III	29	15	8	5†	1	†Three with negative A-Z tests, 2 to 7 months. One with negative uterus after hysterectomy.
IV	49	23	11	11‡	4§	‡Two negative hysterectomies and four negative curettings from uterus. §One died of shock—no autopsy.
V	19	10	3	4	2	
Totals	147	73	36	27	11	92.5% Follow-up

## II. Probably Benign Hydatidiform Moles

(Slight to moderate hyperplasia of trophoblast)

In this group (Figs. 4, B and 5) there were 30 cases, two of whom showed clinical evidence of low grade chorionic malignancy (Table II) of the type characterized as chorionadenoma destruens. Both are alive and well following hys-

terectomy, three and ten years, respectively. Of the remaining 28, only four have insufficient follow-up data, the other 24 being alive and well, with 13 having subsequently become pregnant. Details of these prognostic data are summarized in Table III.

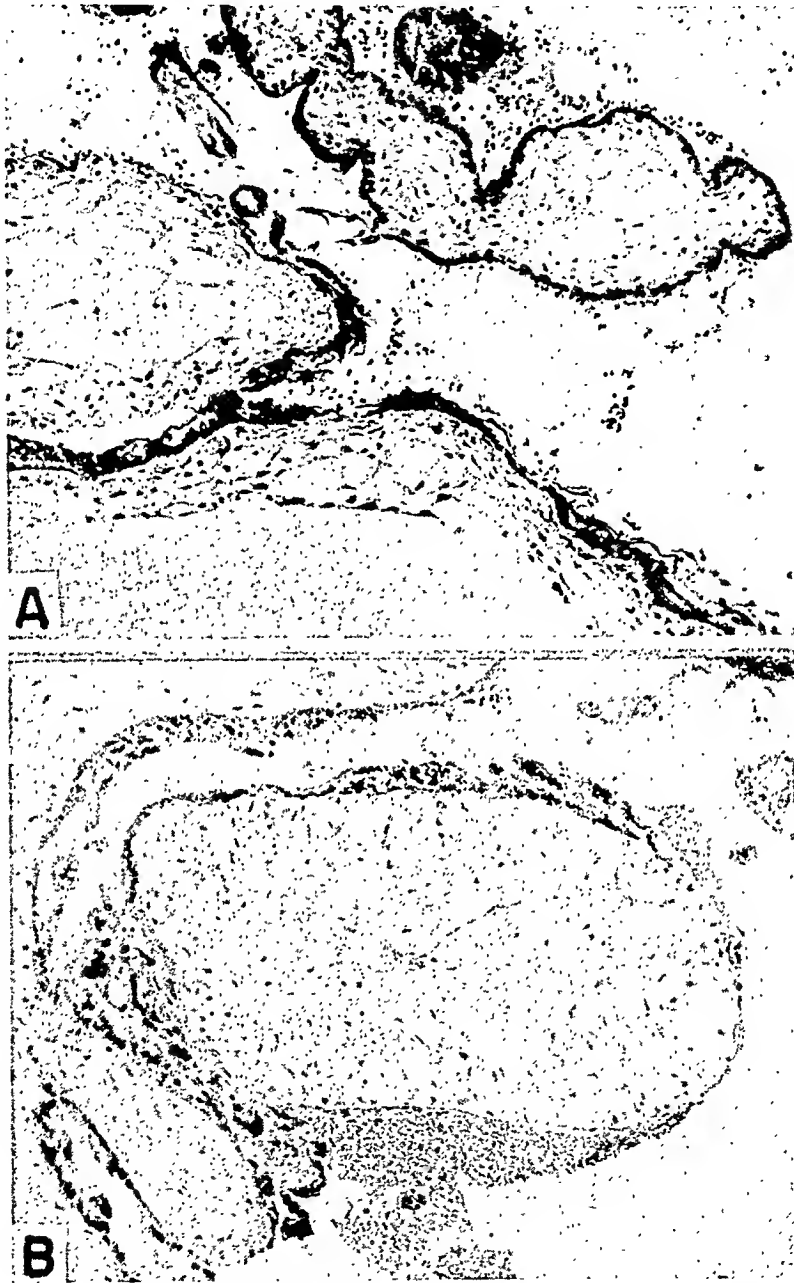


Fig. 4.—A., A benign hydatidiform mole (I) showing portions of three villi in varying stages of hydatid degeneration. The trophoblast is normal or at most only slight hyperplasia. Patient was living and well eleven years later. (M-2,  $\times 110$ .)  
B., A probably benign hydatidiform mole (II) showing moderate trophoblastic hyperplasia, confined mostly to the syncytium. Patient had a baby five years later. (M-52,  $\times 110$ .)

These moles as a group are characterized by slight to moderate hyperplasia of both trophoblastic elements, but no essential evidence of anaplasia. In grading all tumors, there is no sharp line of demarcation between each designated grade. This situation is also true with regard to hydatidiform moles. This group, therefore, represents a gradual transition from the obviously benign moles of Group I, with little, if any, hyperplasia and a good



deal of benign degeneration, to the more disturbing moles of Group III with much hyperplasia and beginning but significant anaplasia. There is some variation in the different specimens of this group, as can be seen by the three examples depicted in Figs. 4, B and 5. There is no evidence of malignant change in the trophoblast of either of these specimens, although the one in Fig. 5 subsequently invaded the uterus. In reappraising this specimen, we felt that it probably should have been placed in Group III, but it is included in Group II as originally graded. It is noteworthy that the villi which were penetrating the uterus were surrounded by a well-differentiated trophoblast which recapitulates

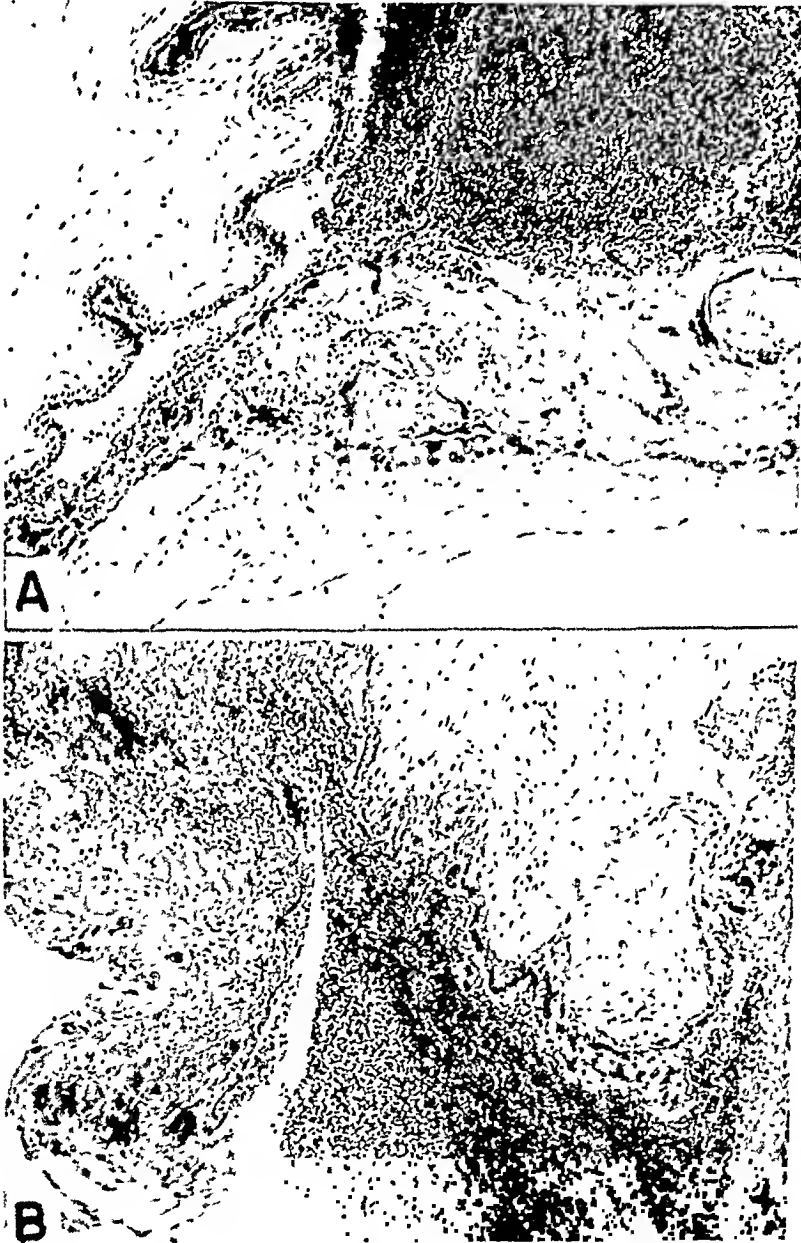


Fig. 5.—A., A probably benign hydatidiform mole (II) showing normal trophoblast on the upper left villus and hyperplastic epithelium on the lower one, the Langhans element of which is slightly anaplastic and the syncytium vacuolated. Patient developed a low grade chorionadenoma destruens, but was well three years later. This mole, in retrospect, perhaps should have been graded higher as possibly benign (III). (M-200,  $\times 110$ .)

B., Same case as above to show fibrinoid degeneration of previously hyperplastic trophoblast toward left. (M-200,  $\times 110$ .)

that of the twelve-day ovum,<sup>5</sup> a stage just prior to the formation of the chorionic villi. It is also of interest that the patient is alive and well three years after the hysterectomy, the latter having been done for a persistently positive Friedman test two and four weeks after the passage of the mole.

This group can, therefore, be summarized as one in which the ever-present threat of chorionic malignancy following hydatidiform mole is just beginning to manifest itself, even though the specimens as a group show little of a disturbing nature in their trophoblast.



Fig. 6.—A., A possibly benign hydatidiform mole (III) with moderate hyperplasia of cytotrophoblast (lower left) and slight anaplasia (upper left). Patient became pregnant fifteen months later, but miscarried. (M-8,  $\times 110$ .)

B., A possibly benign hydatidiform mole (III) with persisting anaplasia within degenerated trophoblast. Patient developed a low grade chorionadenoma destruens, but was well eight years and eight months later. (M-37,  $\times 110$ .)

## III. Possibly Benign Hydatidiform Moles

(Hyperplasia with slight anaplasia of trophoblast)

In this group (Fig. 6) there were 33 cases, of whom four showed clinical evidence of low grade malignancy, the types of which are seen in Table II. Of the four malignancies, one was a syncytial endometritis and three were of chorionadenoma destruens type. The former patient died on the seventh post-operative day of peritonitis, while the other three are living and well two months, two years, and 4 years, respectively. The follow-up data on the chorionic malignancies as a group are shown in Table IV. Of the 29 remaining in this group which were clinically benign, only one has no follow-up data, the other 28 being alive and well, with 15 of them having become pregnant. Details of these prognostic data are summarized in Table III.

TABLE IV. FOLLOW-UP DATA ON CHORIONIC MALIGNANCIES

GRADE	CASES	SUBSEQUENT PREG- NANT	LIVING AND WELL		NO DATA	DIED	PER CENT CURED	REMARKS
			C UTERUS	S UTERUS				
Chorion- epithelioma in situ	7	2	2*	3†	0	0	100	*Living and well; 4 to 5½ years †Two cases living and well; 3 plus years, and remaining one had negative uterus and was living and well 1½ years postoperatively
Syncytial endometritis	3	0	2*	6†	0	1‡	89	*Living and well 7 months and 4 years, respectively †3 cases living and well 3 to 10 months; 3 cases living and well 4 to 9 years ‡Died of sepsis, 7 days postoperatively (hysterectomy)
Chorion- adenoma destruens	32	0	0	27*	4	1†	97	*Living and well 1 to 14 years postoperatively (25 cases, 2 or more years) †Died 5 days postoperatively (hysterectomy) of sepsis
Chorion- carcinoma	5					5*	0	*Four patients died with uterus still in, the fifth not being removed until just before death
Totals	53	2	4	33	4	7	84.6	89% follow-up, excluding 2 postoperative deaths

The moles in this group are characterized by variable amounts of hyperplasia of both trophoblastic elements, together with slight but definite anaplasia, examples of which are seen in Fig. 6. Of the two examples chosen, the one in Fig. 6, A is at first glance more disturbing than the one in Fig. 6, B. However, there is only very slight anaplasia in the former, whereas this feature is more

prominent in the latter. It may be of significance that Fig. 6, *A* represents an ultimately benign mole clinically, whereas Fig. 6, *B* is from a mole that showed evidence of uterine invasion by a relatively well-differentiated trophoblast.

Another malignant mole in this group, the twenty-fifth mole examined by one of us (A. T. H.) up to that time, showed a tissue-culture-like growth of both syncytio- and cytotrophoblast upon the surface of blood clot as seen in

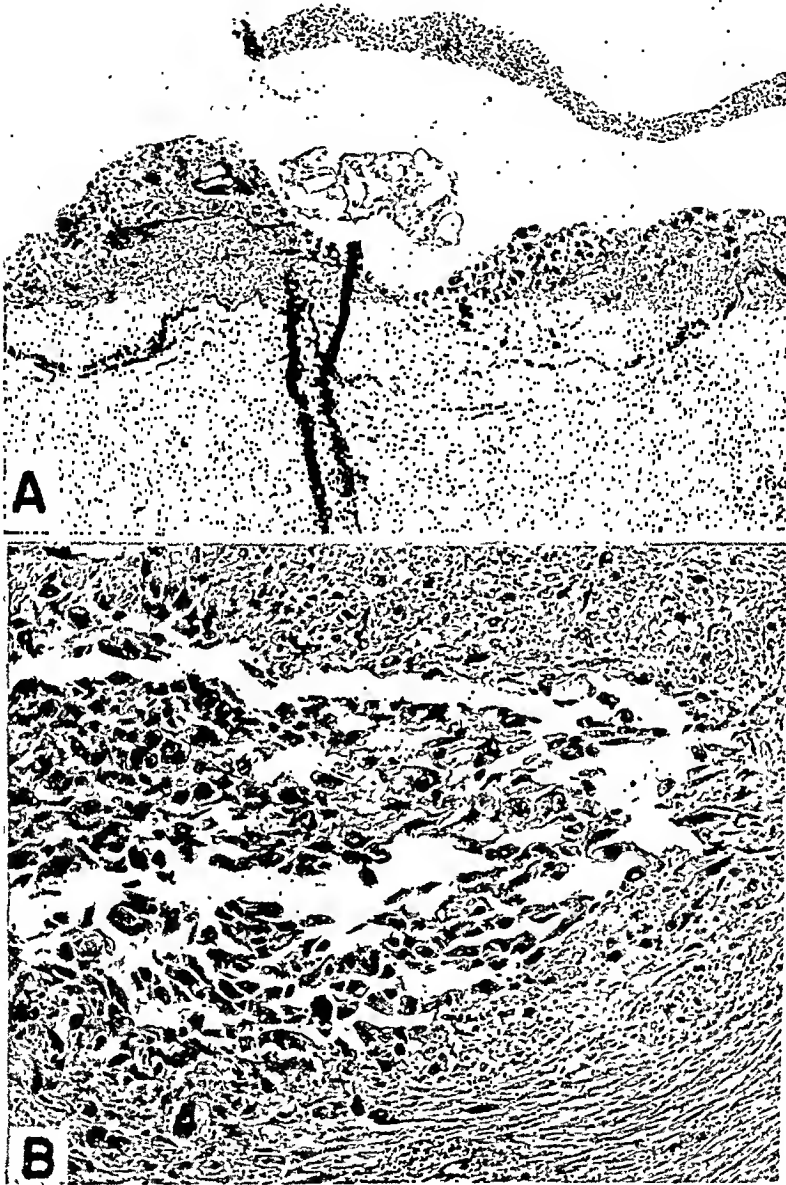


Fig. 7.—*A.*, Tissue-culture-like growth of both trophoblastic elements upon the surface of blood clot. The original mole was possibly benign (III). Patient developed chorionadenoma destruens as shown in Fig. 7, *B.* (M-21,  $\times 50$ .)

*B.*, Uterus showing locally invasive anaplastic trophoblast within myometrium of same case as Fig. 7, *A.* Patient was well two years postoperatively. (M-21,  $\times 125$ .)

Fig. 7, *A.* The mole itself, otherwise, resembled the rest of the group. Since this was the first time in the series such a histologic pattern had been encountered, it was misinterpreted, although the clinician was warned about the potential danger in view of our inability to interpret definitely this finding. Hysterectomy was performed forty-five days after the passage of the mole because of a positive A-Z test performed on the fortieth day. Evidence of clin-

ical subinvolution of the uterus and vaginal bleeding were also present. It is of interest that the uterus showed a relatively undifferentiated nest of tumor within the myometrium, as shown in Fig. 7, *B*. These invading trophoblastic cells resemble those of the 7- to 8-day ovum<sup>7</sup> just after implantation. Most of them are cytotrophoblastic in type, but the larger ones are young syncytiotrophoblastic cells. The patient was alive and well two years postoperatively.

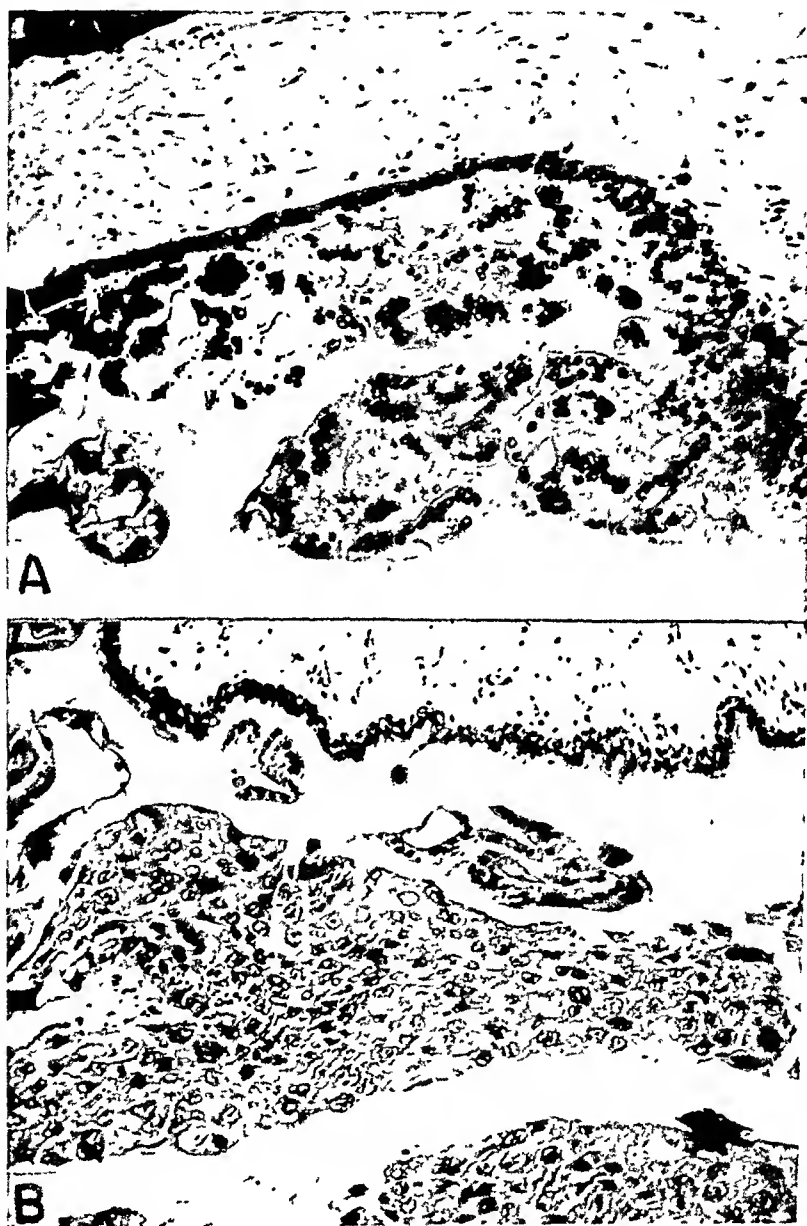


Fig. 8.—*A*, A possibly malignant hydatidiform mole (IV) showing marked syncytiotrophoblastic proliferation with slight anaplasia. Same case as Fig. 8, *B*. (M-88,  $\times 150$ .)

*B*, Same case as Fig. 8, *A*, but showing marked cytotrophoblastic hyperplasia with moderate anaplasia. Patient was well six and one-half years after passage of mole. (M-88,  $\times 150$ .)

This group can, therefore, be summarized as one in which the trophoblast is more abundant and somewhat less differentiated than in the previous groups, features which are reflected in the increasing percentage of ultimate, although low grade malignancy. Also, one encounters for the first time evidence of trophoblastic growth independent of the villi, a feature often associated with ultimate malignancy.

#### IV. Possibly Malignant Hydatidiform Moles

(Variable hyperplasia and moderate anaplasia of trophoblast)

There were 59 cases in this group with 10 malignancies whose grades are shown in Table II. Most of these (eight) were of chorionadenoma destruens type, with one each of syncytial endometritis and chorionepithelioma in situ.

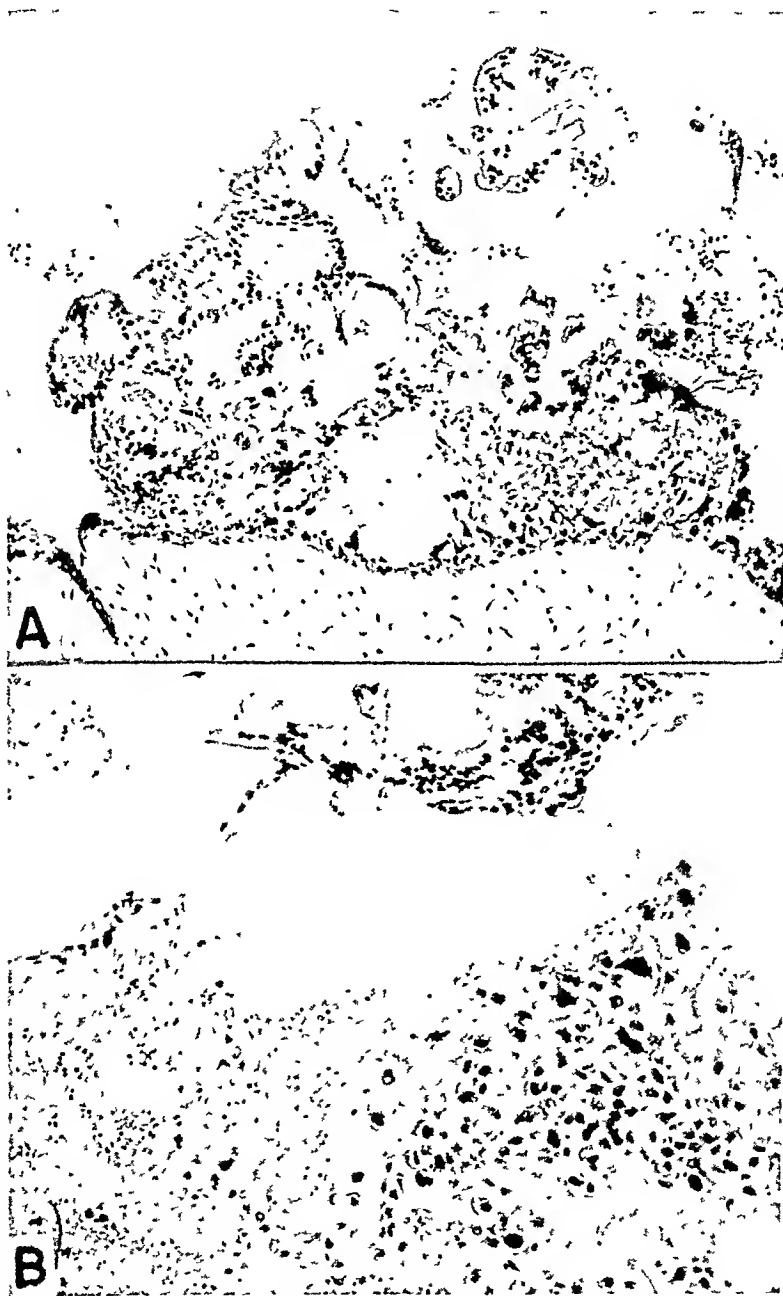


Fig. 9.—A., A possibly malignant hydatidiform mole (IV) with moderate hyperplasia and slight anaplasia of both trophoblastic elements. Same case as Fig. 9, A. Patient developed a low grade chorionadenoma destruens, but was well five years postoperatively. (M-40,  $\times 110$ .)  
B. Same as Fig. 9, A, but showing moderate anaplasia of cytotrophoblast. This is the most malignant area in the entire mole. (M-40,  $\times 125$ .)

The patient with syncytial endometritis was alive and well ten months later, while the one with chorionepithelioma in situ was normally pregnant (verified by x-ray) seven months later. Of the 8 cases of chorionadenoma destruens, one died postoperatively of peritonitis, one had no follow-up, while the re-

maintaining six are living and well from sixteen months (one patient) to eleven years (five from five to eleven years). The patient well five years later had multiple negative Friedman tests postoperatively. It is of interest to note that this patient's uterus showed extension of the low grade tumor process to the surface of the uterus beneath the bladder flap, showing the locally malignant character of this tumor. The general follow-up data on all the chorionic malignancies are summarized in Table IV.

Of the 49 clinically benign moles in this group, there were follow-up data on 45, 23 of which were followed by subsequent pregnancies. The prognostic data in these cases are summarized in Table III.

The significant histologic features of this largest group of moles are seen in Figs. 8 and 9. The abundant growth of both syncytiotrophoblast and cytotrophoblast is evident in both cases here represented. However, their proportions and exact histologic patterns vary with each mole as well as in various portions of the same specimen. For example, the syncytiotrophoblast in each case depicted is exuberant and relatively benign in appearance, but in Fig. 8 it is much less vacuolated than in Fig. 9. These vacuoles represent the embryonic recapitulation of placental intervillous space formation, and first appear in the developing ovum of eight to nine days of age.<sup>7</sup> It is interpreted as evidence of relative benignity even though, on rare occasions, it is associated with a truly invasive mole of the chorionadenoma destruens type. It has never been seen, to our knowledge, in the invasive and metastasizing portions of the fatal variety of chorioncarcinoma.

The cytotrophoblast likewise varies somewhat in appearance, both cases being rather primitive, and simulating that of the seven-day ovum which normally and actively invades maternal tissues.

The clinically benign case, shown in Fig. 8, possesses, in general, rather more abundant trophoblast than that of the clinically malignant mole in Fig. 9, yet they differ little in their degree of essential anaplasia. However, the malignant case shows some tissue-culture-like growth as seen in Fig. 9, B. The ultimately invasive trophoblast is still morphologically less differentiated than any portion of its parent mole, aside from its obvious ability to invade the uterus. These two cases thus epitomize the increasing general activity and anaplasia of the trophoblast in this, as compared to the previous group, an expression of which is the rising percentage (17 per cent) of malignancies. The two specimens also illustrate how impossible it is in any given case of mole to give it a definitely benign or malignant prognosis. This difficulty becomes less in the two remaining groups, as shown in Fig. 2.

## V. Probably Malignant Hydatidiform Moles

(Variable hyperplasia and marked anaplasia of trophoblast)

This group of 39 cases contains 20 patients who ultimately developed malignancy of one grade or another, and 19 who remained clinically benign. The grades of subsequent chorionic malignancy are summarized in Table II. It is apparent from the relatively high proportion and variety of malignancies that this is an important and dangerous group of moles. The follow-up data on the benign and malignant group are summarized in Tables III and IV, respectively. The ultimate prognosis on the clinically benign group is excellent, with only two patients of the 19 untraceable; ten of the group subsequently became pregnant. The malignant group also has a good prognosis, except for the three with chorioncarcinoma, all of whom died within two years of the passage of the mole.

The striking thing about this group as a whole, two examples of which are seen in Figs. 10 and 11, is the marked anaplasia. There is often a good



deal of benign hyperplasia as well, although this may be quite variable. The trophoblast tends to be of a single indifferent or primitive variety, rather than being sharply divided into the syncytial and Langhans types. The indifferent trophoblast, such as seen in all the examples here shown, tends to resemble that of the implantation pole of a very recently embedded ovum.

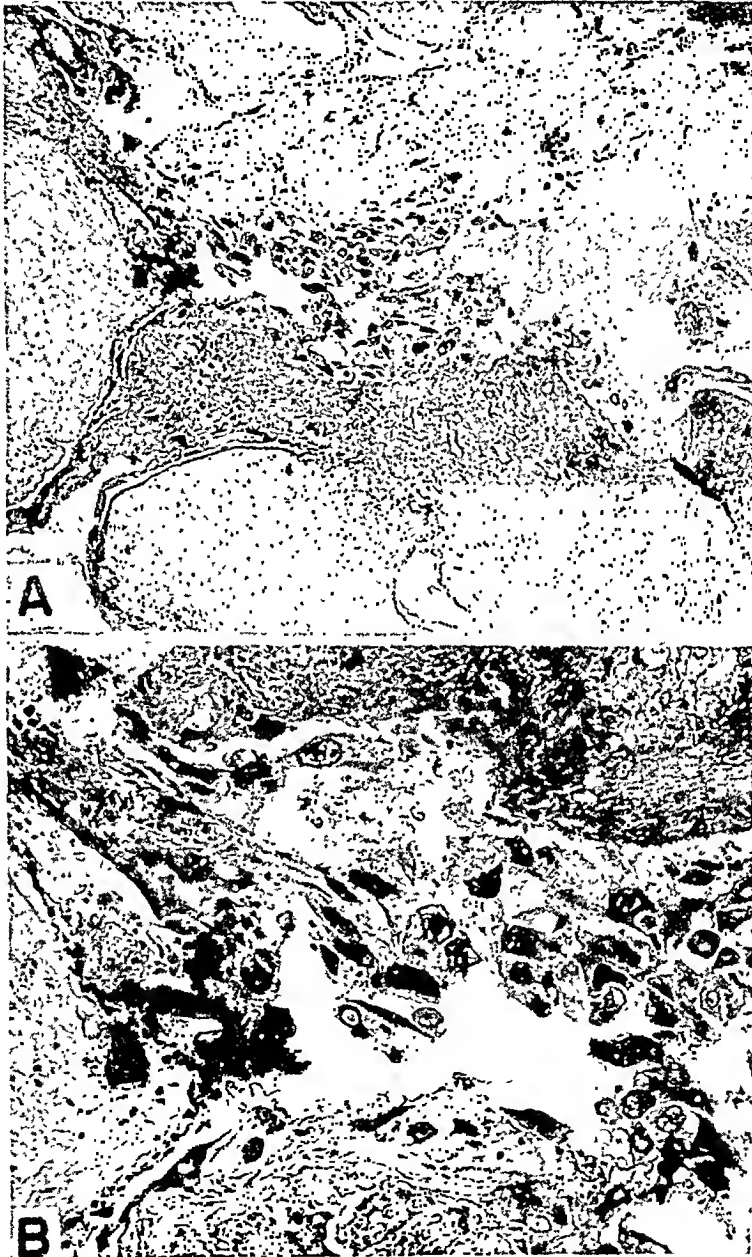


Fig. 10.—A., A probably malignant hydatidiform mole (V) to show highly anaplastic trophoblast amid an area of fibrinoid degenerated trophoblast. Patient was well one and one-half years later. Same case as Fig. 10, B. (M-179,  $\times 50$ .)  
B., Higher power detail of same trophoblast shown in Fig. 10, A. (M-179,  $\times 150$ .)

Here the trophoblast is indifferent, or, as we have chosen to call it, "admixed," because the syncytio- and cytotrophoblastic cells have no particular arrangement, and also may differ little from each other in this primitive phase of their development. However, as the early syncytiotrophoblastic cell differentiates, it becomes larger, darker, more irregular, and possesses a hyperchromatic nucleus. The latter, by budding, produces a multinucleated structure which characterizes syncytium throughout the remainder of its life. Fig. 10



shows an excellent example of this anaplastic epithelium that resembles in many details the normal primitive trophoblast of the early implanting ovum. It is interesting that the patient from whom this specimen was received is alive and well one and one-half years after the mole was passed.

Another feature of interest and probable importance in this group is the loss of basement membrane associated with the adjacent anaplastic trophoblast. A more marked degree of this phenomenon is present in cases of trophoblastic invasion of the villous stroma seen in some cases of malignant moles. Reference will be made to this point later. The patient from whom this specimen was obtained developed a chorionadenoma destruens, and came to hysterectomy five days after the passage of the mole. Unfortunately, follow-up data are available on this patient for only four months, after which she failed to return to the hospital. Her local physician was contacted, but his records of twenty-four years ago were not adequate to trace the patient.

The second case illustrating this group (Fig. 11) is not essentially different from any of the others from a morphologic standpoint, although the patient died from chorioncarcinoma within a year after passage of the mole. Only two sections of the mole were available and curettage had been done. Therefore, the uterus had not been removed. It has been noted by various authors<sup>2, 7, 13, 15</sup> that many cases of fatal chorioncarcinoma show little if any tumor in the uterus. The above, at autopsy, did show a single hydatid villus attached to the myometrium by innocuous appearing trophoblast, as seen in Fig. 11, *B*. The degree of trophoblastic anaplasia does not approach that of even an invasive mole, let alone that of a chorioncarcinoma. It appears, therefore, that the metastases which killed the patient gained early entrance to the maternal vascular system during the growth of the mole, although this point is not capable of proof from the data available.

The probably malignant moles, in summary, seem to justify their designation, because all of them appear extremely anaplastic and capable of invading the uterus or metastasizing to distant sites, even though only half of them ultimately do so.

## VI. Malignant Hydatidiform Moles

(Exuberant hyperplasia and marked anaplasia  
of trophoblast, often invading the endometrium)

This small group of 17 cases all showed various degrees of morphologic and/or clinical malignancy. The distribution of these cases among the various grades of chorionic malignancy is shown in Table II. Examples of these various grades, all originally diagnosed as malignant, are seen in Figs. 12 to 21. The prognosis of the patients in this group is good, except for the two cases of fatal chorioncarcinoma, who were dead ten and sixteen months, respectively, after passage of the mole. The general follow-up data on all the various grades of chorionic malignancy are given in Table III.

### A. Chorionepithelioma in Situ

(Morphologic malignancy plus endometrial invasion)

Of the seven cases in this general group (Table II), five were originally called malignant and put in Group VI from the examination of the mole alone. The other two were placed in Groups IV and V, respectively. Their ultimate grading as chorionepithelioma in situ, irrespective of their original molar groups, was based on evidence of endometrial invasion. Such criteria were obtainable only from the removed uterus or adequate sections from the endometrium of the placental site. The designation for this small group of locally invasive, apparently malignant tumors, has been coined by us to include what we con-

sider a bona fide grade of chorioma. Whether it represents an early and, therefore, curable stage of true chorionepithelioma, we cannot say. Two examples of this highly malignant-appearing tumor are seen in Figs. 12 and 13. Both show evidence of exuberant trophoblastic overgrowth with pleomorphism and loss of basement membrane at the junction of the epithelium and stroma.

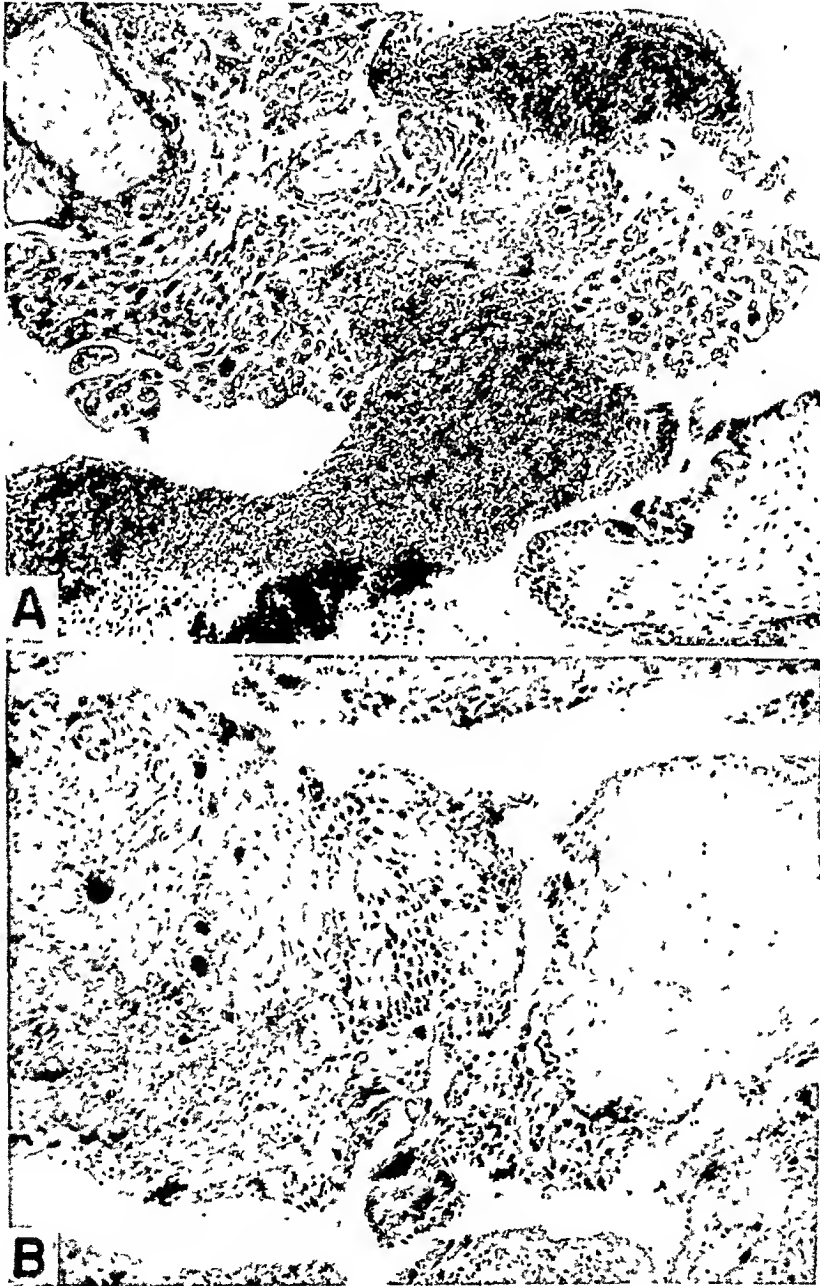


Fig. 11.—A., A probably malignant hydatidiform mole (V) to show marked anaplasia and beginning tissue-culture-like growth of trophoblast. Patient developed chorioncarcinoma and died "within a year." Same case as Fig. 11, B. (M-100,  $\times 110$ .)  
B., Same case as Fig. 11, A to show placental site from uterus obtained at autopsy. Note relatively benign trophoblast attached to villus (right) and myometrium (left). This may be one of the rare examples of fatal chorionadenoma destruens, although the material available did not settle this point. (M-100,  $\times 110$ .)

The latter is invaded by its own trophoblast in the specimen shown in Fig. 12, although the epithelium itself is not quite so malignant in appearance as that seen in Fig. 13. However, both specimens showed definite invasion of the endometrium, one example of which is illustrated in Fig. 13, B, and possessed the over-all morphologic criteria of chorionic malignancy. It is of interest to

note that the patient who passed the first mole is alive and well four years after its passage, while the second patient become normally pregnant one year later. Data on her delivery are not available.

### B. Syncytial Endometritis

(Accentuation of syncytial placental site  
giant cells plus chronic infection)

This term represents the lowest grade of chorionepithelioma in all the standard classifications<sup>2</sup> of this type of tumor. We are in doubt as to whether it is a bona fide evidence of chorionic malignancy, although we include it as such in this study.

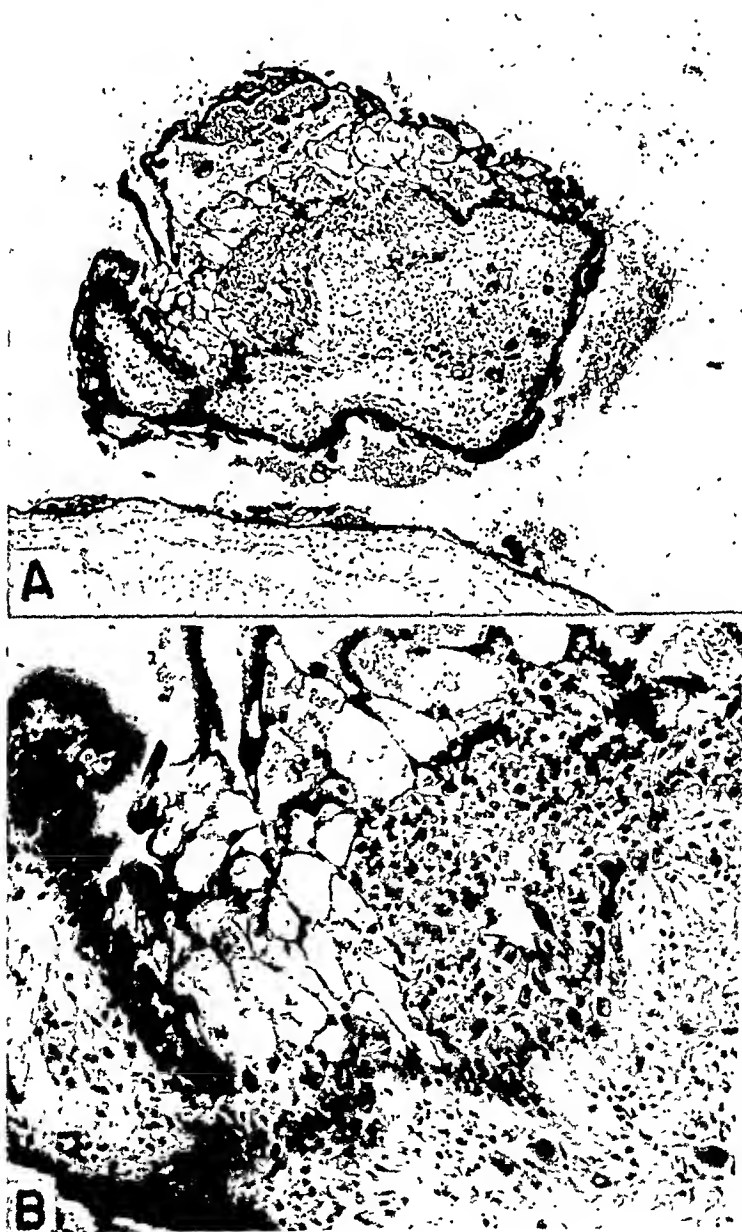


Fig. 12.—A., A malignant hydatidiform mole (VI) to show marked growth and anaplasia of trophoblast with the latter invading its own stroma. Same case as shown in Fig. 12, B. Endometrium showed invasion by malignant appearing trophoblast constituting a chorionepithelioma in situ, but patient was well five years and seven months later. (M-10,  $\times 50$ .)

B., Same case as Fig. 12, A, but in higher detail. Note loss of epithelial basement membrane and villous stroma invaded by its own trophoblast. (M-10,  $\times 150$ .)

Of the nine cases in this general grade (Table II) only four were originally placed in the malignant Group (VI), the remainder having been placed in either Groups III, IV, or V. Their ultimate inclusion into this grade of malignancy is again based on evidence of myometrial invasion by the syncytial giant cells of the placental site (Fig. 14). That this type of invasion of the uterus by trophoblast does not always constitute true malignancy is shown by the case here illustrated. The patient in question passed a mole which we placed in Group VI. A subsequent curettage done on the sixteenth postpartum day yielded only a few fragments of myometrium and a little necrotic decidua. One of the myometrial fragments was from the placental site, and showed the

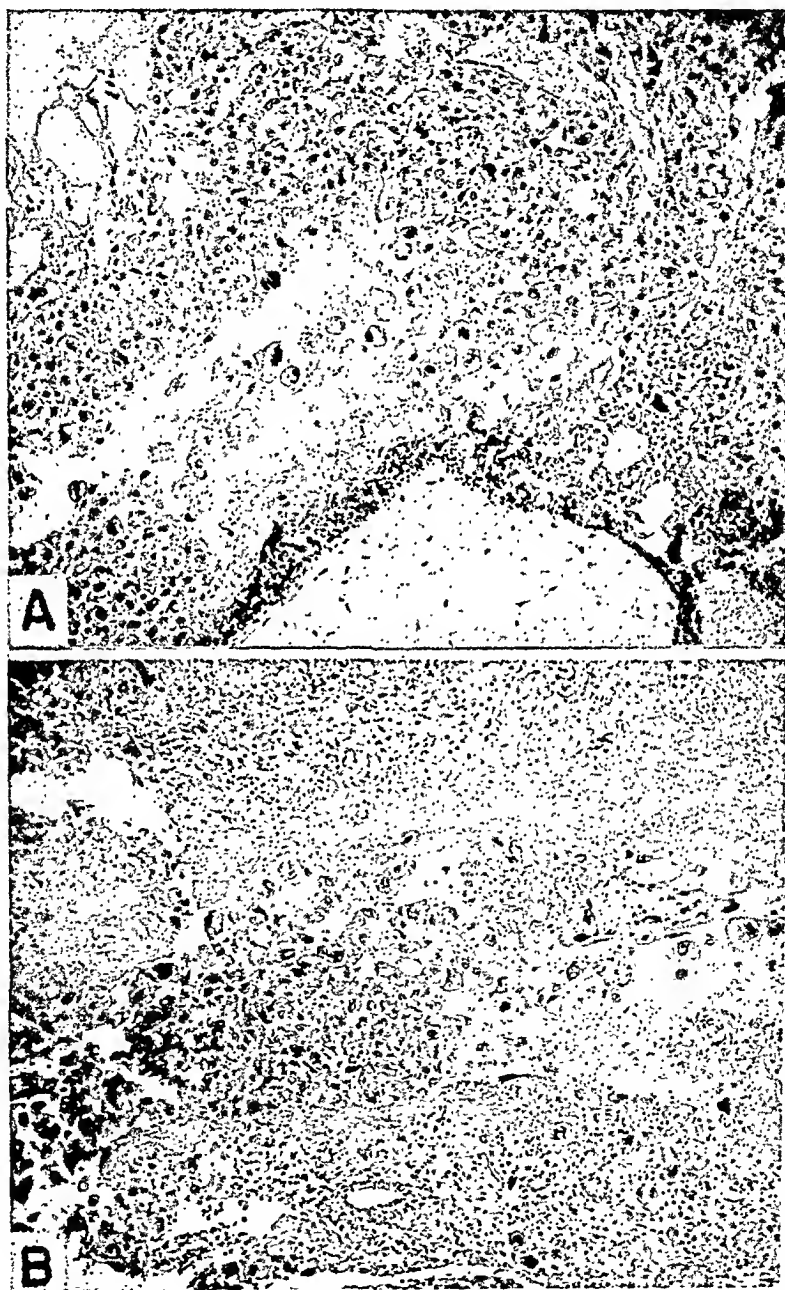


Fig. 13.—A., A malignant hydatidiform mole (VI) with exuberant trophoblastic hyperplasia and anaplasia—the latter most marked in the cytotrophoblast. Same case as Fig. 13, B. (M-103,  $\times 75$ .)

B., Same case as seen in Fig. 13. A, but showing endometrial invasion by anaplastic trophoblast similar to that of mole itself. This constitutes a chorionepithelioma *in situ*, and yet the patient was normally pregnant one and one-half years later. (M-103,  $\times 130$ .)

picture seen in Fig. 14. A diagnosis of syncytial endometritis was returned and hysterectomy advised because of the malignant connotation implied by the term. The patient refused operation, but was living and well four years later. The case seemed so important to us that one of us personally visited the patient since she had refused to return to her original hospital. It would seem, at least in this instance, that the lesion in question does not constitute a true chorionic malignancy.

Whether such a lesion would ever go on to true clinical malignancy with continued invasion of the uterus and/or metastasis, we do not know. Of the 9 patients in this general grade, two are alive and well with their uteri seven

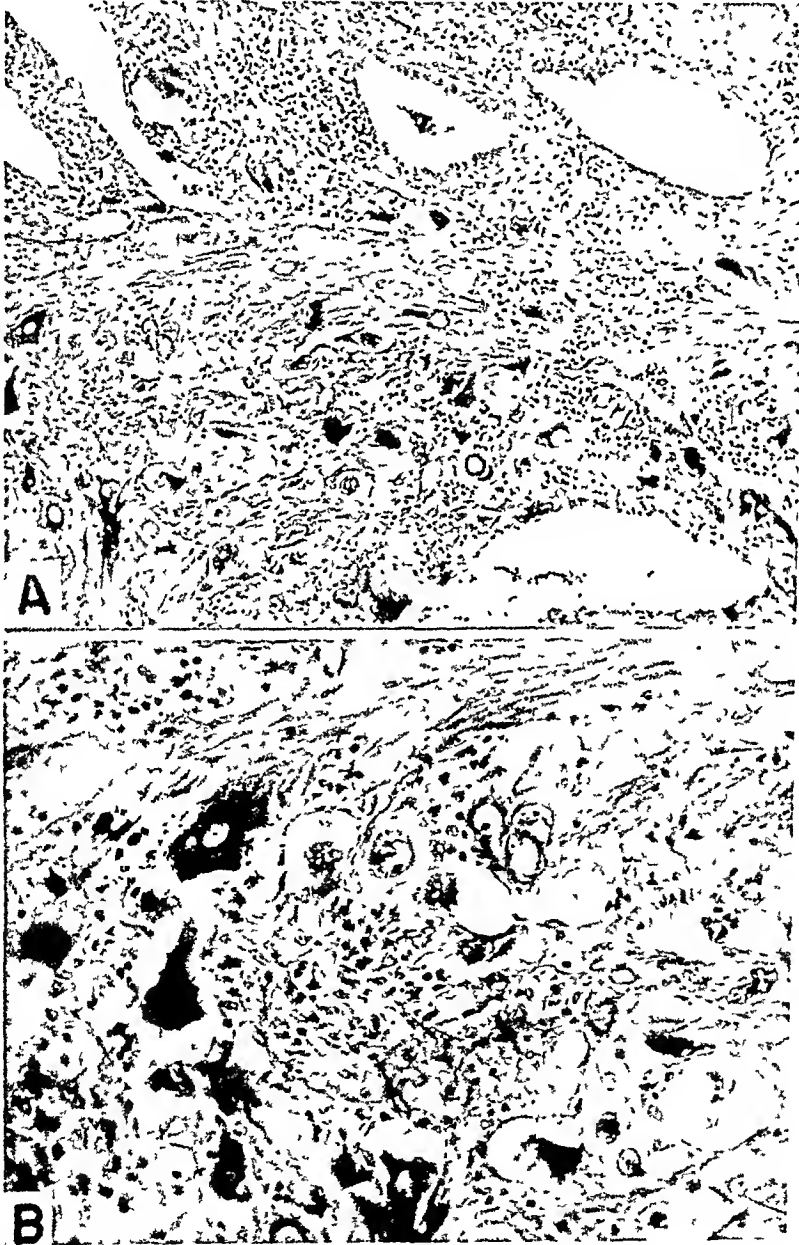


FIG. 14.—A., The placental site illustrating syncytial endometritis curetted from a uterus which had previously contained a malignant mole (VI). Patient was alive and well four years and two months later with intact uterus. Higher power detail is seen in Fig. 14, B. (M-49,  $\times 110$ .)

B., Same region of placental site from case shown in Fig. 14, A. These malignant-appearing syncytial giant cells are only slightly more anaplastic than those of a normal placental site. Note chronic inflammation. (M-49,  $\times 250$ .)

months and four years, respectively, after delivery of the mole; the remaining seven all having had a hysterectomy. One patient died postoperatively of peritonitis, but the remaining 6 are alive and well three months to nine years later (Table IV). This is admittedly not a large series, although it would seem to us to indicate that the lesion is not often, if ever, truly malignant.

If this is a true but very low grade tumor and is merely an exaggeration of the picture seen in the normal placental site throughout pregnancy (except for the secondary chronic inflammation), it may offer a possible explanation of the rare chorioncarcinomas that are known to follow normal pregnancy, abortion, and ectopic pregnancy.

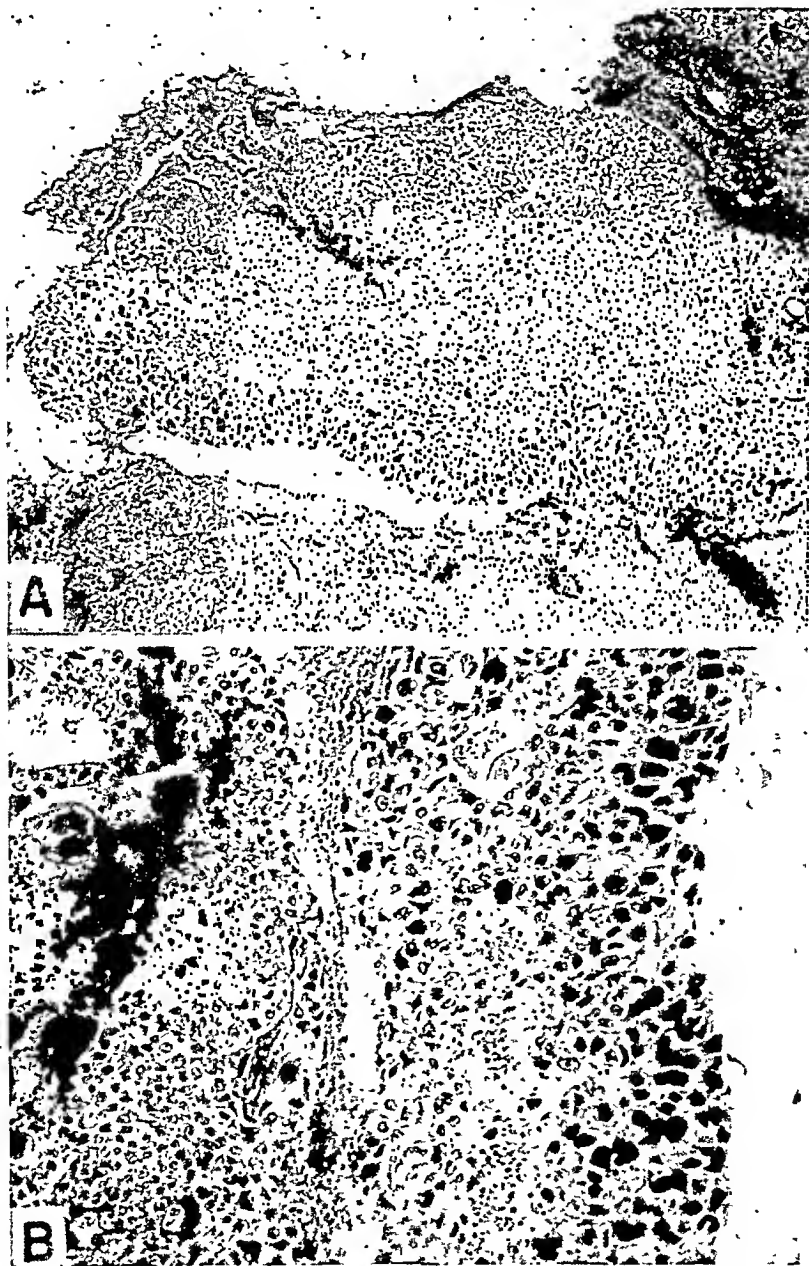


Fig. 15.—A., Curettings obtained at time of evacuation of malignant hydatidiform mole (VI) showing markedly hyperplastic and neoplastic trophoblast. Latter shown at higher magnification in Fig. 15, B. Second curettage done five weeks later showed similar tissue. Uterus removed immediately and showed typical chorionadenoma destruens (see Fig. 15), but patient is still alive over ten years later. (M-16,  $\times 50$ .)

B., Same trophoblast as seen in Fig. 15, A, but at higher magnification. Note extreme variation in degree of trophoblastic differentiation. (M-16,  $\times 150$ .)



### C. Chorionadenoma Destruens

(Invasion of myometrium by malignant mole but without metastasis)

This is the designation used to cover the group of chorionic malignancies which are characterized pathologically by persistent invasion of the myometrium by low grade malignant trophoblast, usually still attached to its parent villus. These tumors rarely, if ever, give rise to clinical evidence of metastasis and, therefore, the prognosis is excellent, provided the uterus is removed (Table IV). This group is characterized clinically by variable amounts of uterine subinvolution, postmolar vaginal bleeding, and usually a persistently

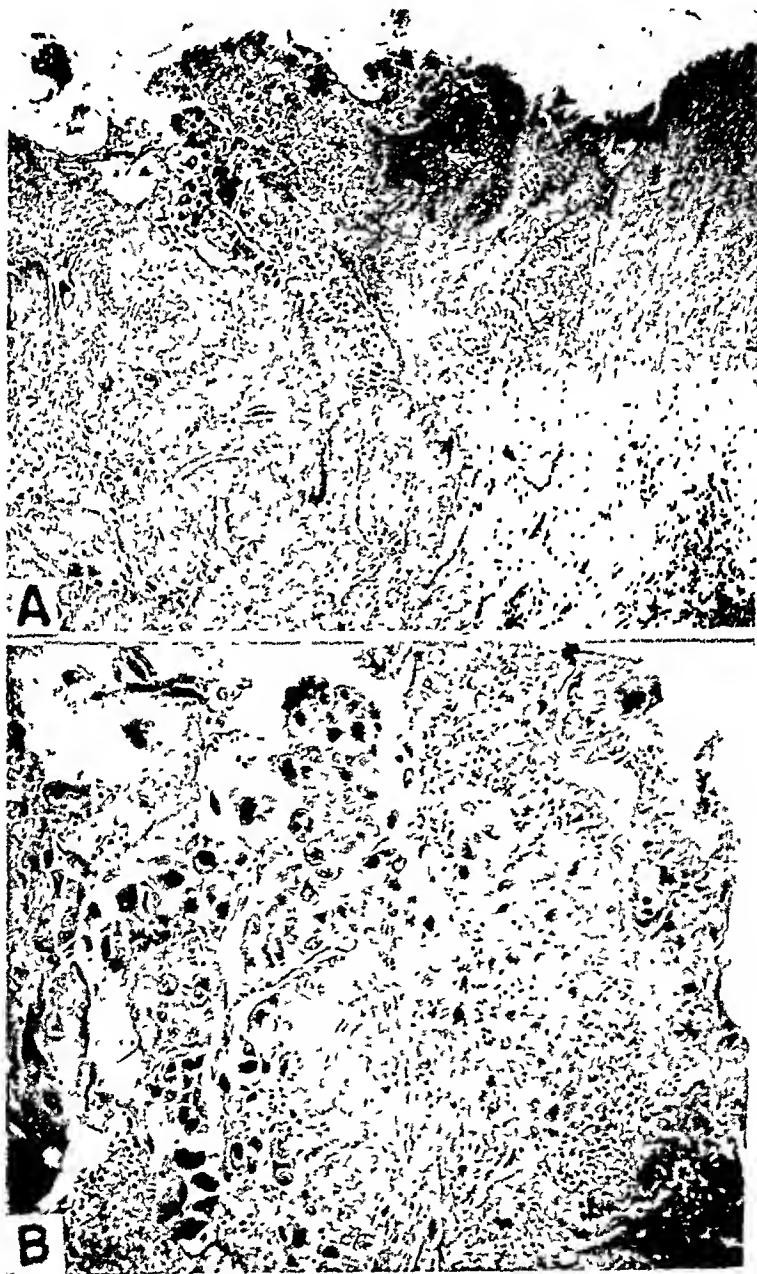


Fig. 16.—A., Uterus from same case as seen in Fig. 15. Low power view of placental site to show invasion of myometrium by malignant-appearing trophoblast. The latter also lies partly with a vessel which opens into the uterine cavity. Higher power detail seen in Fig. 16, B. (M-16,  $\times 50$ .)

B., Same placental site as shown in Fig. 16, A, but in more detail to show markedly anaplastic trophoblast. Patient is still alive over ten years later. (M-16,  $\times 130$ .)

positive test for chorionic gonadotropic hormone. The rare perforating mole belongs in this category, of which we have one in this entire series of 200 cases. (The mole was morphologically malignant [Group VI] and perforated the uterus forty days after its passage, the patient being alive and well two and one-half years postoperatively.)

Of the 17 patients in the series originally diagnosed as having a malignant mole (Group VI), six were ultimately shown to possess chorionadenoma destruens (see Table II). Figs. 15 to 18 show the various pathologic features of this group. The moles are characterized by exuberant overgrowth of trophoblast (Fig. 15) with marked variation in its degree of differentiation. There



Fig. 17.—A typical example of a postmolar uterus showing a chorionadenoma destruens. The organ has been opened laterally, exposing the placental site at the fundus. The posterior wall has also been incised, one portion turned laterally to expose the blood-filled cavity made by the invasive hydatidiform mole. The deep seated lesion—inaccessible to the curette—may account for the low grading on this original mole, i.e., possibly malignant (Group IV). The microscopic appearance of this uterine lesion is seen in Fig. 18. (M-7,  $\times\frac{2}{3}$  natural size.)

is often much benign hyperplasia with transitions to neoplasia. Such variations often occur in the same microscopic field (Fig. 15, B), a feature we have termed the “spread” phenomenon. When it occurs in any mole, we always place the specimen in the malignant group (VI) unless it is confined to only a few cells. The uterus from this same case shows invasion by similar tissue as seen in Fig. 16. The patient whose specimen is shown in Figs. 15 and 16 was alive and well ten years after hysterectomy. An example of a gross uterus



showing this process is seen in Fig. 17. Although the original mole was only a Group IV (possibly malignant) it is included here to show a typical gross uterus with this lesion. The latter is characterized by one or more hemorrhage nodules within the myometrium beneath the placental site. Hence the curette may not always reach the tumor. The cut surface of such an area often reveals a circumscribed cavity containing fluid and clotted blood. At the periphery of such a cavity is the invasive trophoblast responsible for the lesion (Fig. 18). Hydatid chorionic villi are often still attached to this epithelium or are lying free within the cavity. Because of the ultimate benign prognosis



Fig. 18.—A., A general view of the wall of a cavity within the myometrium of a uterus which is the seat of chorionadenoma destruens (see gross uterus in Fig. 17). Note both types of trophoblast, both only moderately anaplastic, but nevertheless invading the myometrium. The associated villus is not shown. Higher power detail of another portion of the lesion is seen in Fig. 18, B. This patient died five days postoperatively of peritonitis, so no follow-up data are available. (M-7,  $\times 50$ .)

B., Markedly anaplastic trophoblast invading the myometrium from same case as shown in Figs. 17 and 18, A. (M-7,  $\times 150$ .)

in such cases, providing a hysterectomy is performed, Ewing has designated this as chorionadenoma destruens. This highly descriptive term could be paraphrased as an "invasive mole." It rarely, if ever, metastasizes. In our entire series, 32 of the ultimate malignancies were of this type. None of the patients have died of chorionic malignancy (Table IV), although we have two or more years follow-up data on only 25 cases, roughly, 78 per cent. There was one postoperative death from peritonitis included in the 7 cases on which there

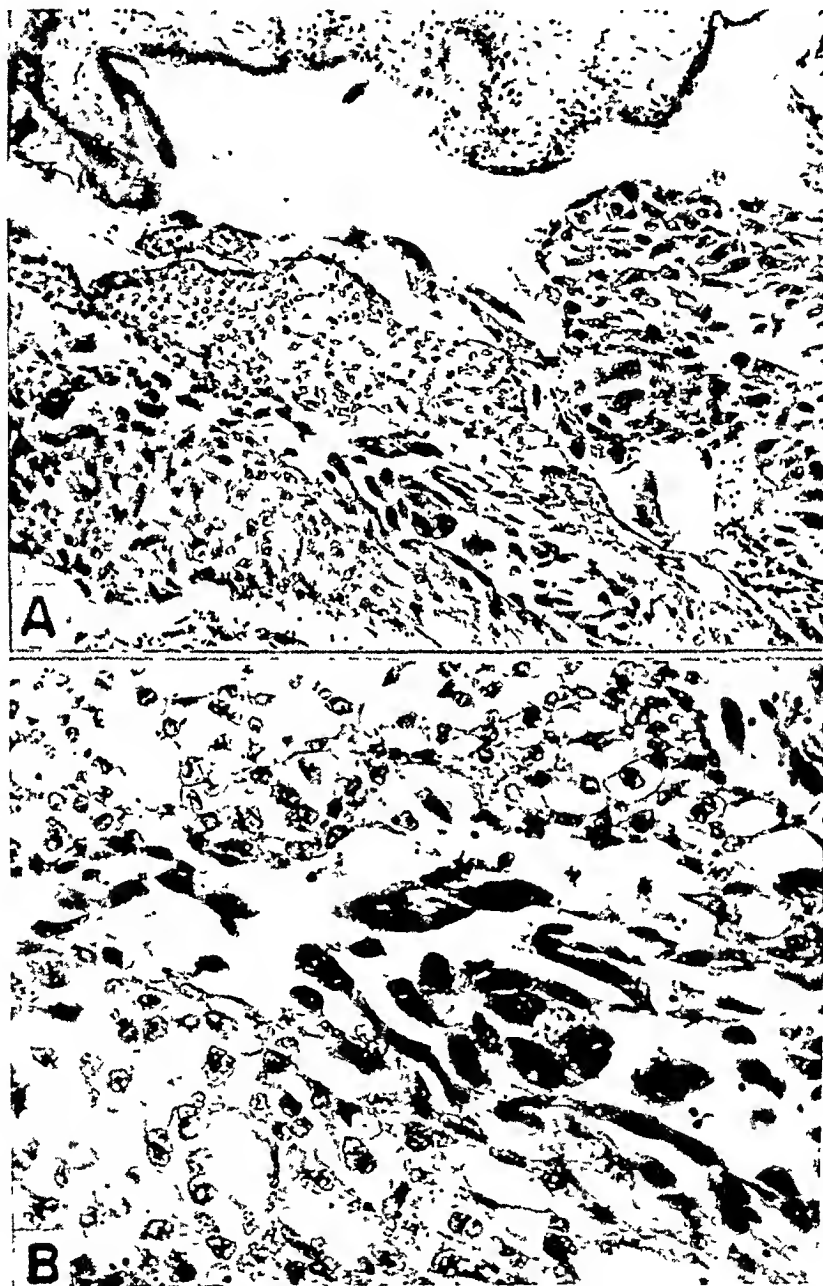


Fig. 19.—A., A malignant hydatidiform mole (VI) showing marked hyperplasia of cytotrophoblast (middle left) and actual neoplasia of both trophoblastic elements (to the right and below). This is one of the two moles giving rise to chorioncarcinoma whose original mole or curetting showed a histologic pattern consistent with chorioncarcinoma. The patient was dead of brain metastasis within ten months. See Fig. 19, B for higher power detail of this trophoblast. (M-191,  $\times 110$ .)

B., Same trophoblast as shown in Fig. 19, A. The hyperplastic trophoblast is seen in the upper portion of the photograph, whereas the neoplastic features of both elements are seen below. This picture is indistinguishable from the brain metastasis of the same patient as seen in Fig. 20, A. (M-191,  $\times 250$ .)

are insufficient data to absolutely exclude the possibility of ultimate chorionic metastases. The two-year follow-up limit was arbitrarily set because all of our cases of chorioncarcinoma died within two years following the passage of the mole. This is in general agreement with the literature,<sup>20</sup> although various authors cite individual cases of death from this cause as late as eighteen years after the mole was delivered. These cases are a distinct rarity, even in a rare disease, and so may be disregarded for all practical purposes.

#### D. Chorioncarcinoma

(Variable picture in uterus but invariable metastases cause death)

This is the term used to describe the rare, fatal chorionic malignancy that may follow any form of pregnancy, but is most common (about 50 per cent) following moles. It is distinguished pathologically by metastases commonly to the lungs, brain, and vagina, but may involve other viscera. The metastases are pure chorionic epithelium without other villous elements, and possess a plexiform pattern of undifferentiated cytotrophoblast, the masses of which are more or less covered by immature syncytiotrophoblast. The uteri at autopsy often give no clue as to the highly malignant nature of the tumor. This fact has accounted for many references in the literature<sup>2, 13, 15, 17</sup> to fatal chorionepithelioma associated with disappearance of the primary tumor from the uterus. Indeed, three of our five fatal cases of this grade of chorionic tumor failed to show any true evidence of primary tumor at autopsy. A distressing feature in many of these cases is the lack of evidence on uterine curettage of the highly malignant nature of the tumor; as a result, the patient often dies with her uterus still intact. The moles from these patients, however, all show a high degree of morphologic malignancy, as shown by the fact that all 5 of our cases were placed in either Group V or Group VI, i.e., probably or definitely malignant. Whether even immediate hysterectomy would save these patients is a moot question, for Ewing<sup>2</sup> states that he has never seen a clinically cured case of true chorioncarcinoma. They, therefore, appear to be coincidentally malignant with respect to the pregnancy from which they arise. The various histologic characteristics of chorioncarcinoma are represented in Figs. 19 to 21.

The highly anaplastic nature of the original molar trophoblast is seen in Fig. 19. The mole was originally diagnosed by us as a VI, although what the original pathologist thought of it is not clear from our records. Unfortunately, the patient was lost track of after a negative curettage one month later. Follow-up data on her death were obtained from the medical examiner who performed a medico-legal autopsy nine months later. The metastasis to the brain is shown in Fig. 20, A. It is characterized by the typical plexiform masses of malignant cytotrophoblast covered by immature syncytiotrophoblast. (The morphology of metastasis varies from case to case, although in general they resemble the one shown. Those in the brain tend to be most photogenic, because their morphology is not obscured by blood.) The uterus in this case (Fig. 20, B) typifies the negative or equivocal character of the placental site in such cases. No tumor worthy of the name—certainly not a chorioncarcinoma—was found, although the vessels contained trophoblast undergoing fibrinoid degeneration. Whether this constitutes residual tumor we are not able to say. It certainly does not in any way resemble the metastases which caused the death.

In our series of 200 moles, five were followed by this form of tumor (Table II) although only two were originally placed in Group VI, the other three having been diagnosed as Group V. In one of the three latter cases we obtained material on both the mole and the curettings, the former showing a

Group V and the latter (Fig. 21) a Group VI morphology. Because we are attempting to correlate moles per se, we diagnosed this (mole), as only probably malignant, even though the curettings were highly malignant. In our experience, this and the previous one are the only two moles in the entire series of 200 whose original morphology or curettings are similar to the ultimate metastases which kill this type of patient.

All of our cases of chorioncarcinoma died as the result of their metastases within two years of the passage of the mole, the actual intervals being ten months, eleven months, "within a year," sixteen months, and two years,

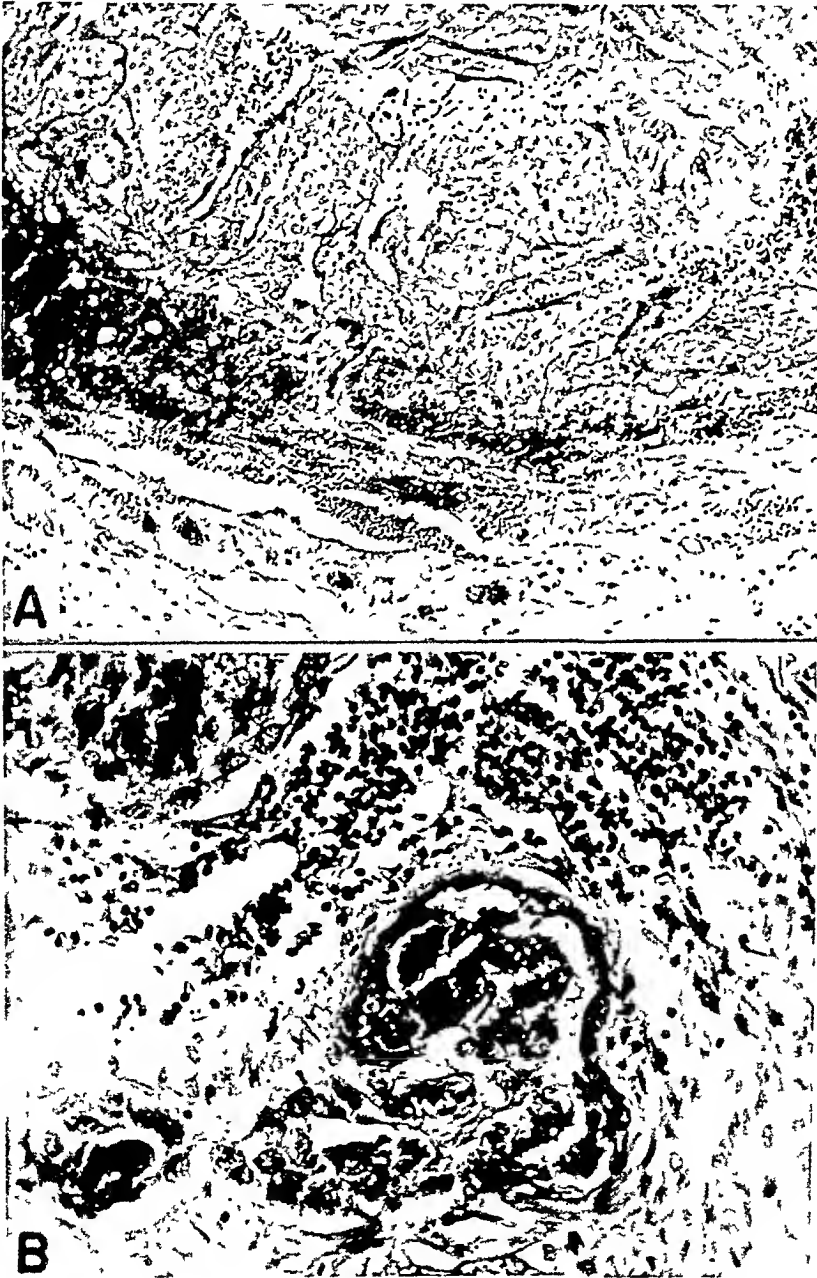


Fig. 20.—A., Brain metastasis of chorioncarcinoma from same case shown in Fig. 19. Note identical morphology of metastasis and original molar trophoblast. Brain tissue is seen in the lower portion of the photograph. Same case as seen in Fig. 20, B. (M-191,  $\times 110$ .)

B., Placental site from uterus obtained at autopsy of patient dying from chorioncarcinoma. Same case as illustrated in Figs. 19 and 20, A. This vessel contains trophoblast which is the seat of fibrinoid degeneration, but does not in any way resemble the trophoblast of the original mole or its metastases. (This case epitomizes the often negative or equivocal picture in the uterus of patients dying of chorioncarcinoma.) (M-191,  $\times 250$ .)

respectively. Four of the five patients died with their uteri still intact, the fifth having had a hysterectomy about two years after the mole or a month prior to death. Of four patients who had a known uterine curettage within a month after the mole, two were definitely negative, one apparently not alarming, and only one showed evidence of tumor; and yet that patient did not come to hysterectomy, apparently because the original pathologist was not disturbed by what he saw in the curettings (Fig. 21). The other patient had no curettage after the mole, but the original pathologist was apparently not disturbed by what he saw in the mole (Fig. 11, A), for the patient did not come to hysterectomy. Curettage, therefore, seems to have been of little help



Fig. 21.—A., Curettings of malignant mole (VI) obtained the day following the spontaneous delivery of a probably malignant hydatidiform mole (V). This is the second instance of original molar tissue resembling morphologic chorioncarcinoma. High power detail is seen in Fig. 21, B. Patient died one year later of chorioncarcinoma. (M-169,  $\times 110$ .)

B., Higher power detail of malignant trophoblast from case shown in Fig. 21, A. Note benign-appearing villus at upper left. The large pale epithelial cells are malignant cytotrophoblast while the occasional dark cells are syncytiotrophoblast. (M-169,  $\times 250$ .)

in making a correct diagnosis in our small series of chorioncarcinomas, although in one case (Fig. 21) it might have been. Furthermore, the equivocal or negative picture in the three uteri at autopsy, only two of which are illustrated (Figs. 11, *B* and 20, *B*), on which we have definite information, leads us to doubt whether even immediate hysterectomy would have cured any of these five patients. The possible exception is the case who showed residual tumor a month before her death. It will be recalled, however, that the curettage was not disturbing enough to indicate immediate hysterectomy. Unfortunately for our series, slides of that curettage were not available to us for study.

### Discussion

From a general consideration of the data on these 200 hydatidiform moles there is shown to be a general correlation between the morphologic appearance of the original specimen and/or curettings and the subsequent development of some grade of chorionic malignancy. In other words, the more malignant the trophoblast of the original mole, the more chance the patient has of developing some grade of chorionepithelioma. These may vary from the locally invasive, morphologically malignant chorionepithelioma in situ with an excellent prognosis to the highly malignant, uniformly fatal chorioncarcinoma. This pathologico-clinical correlation is true, irrespective of whether all grades of ultimate malignancy or only the clinically malignant varieties of chorionadenoma destruens and chorioncarcinoma are considered.

In spite of the general correlation noted above, there is no absolute correlation in any individual mole between its original trophoblastic morphology and its histologic or clinical malignancy. Most of the clinically malignant grades, i.e., chorionadenoma destruens and chorioncarcinoma occur, however, in Groups IV, V, and VI, whereas all of the chorioncarcinomas are found in either Groups V or VI. With a large number of slides, carefully selected from many portions of the mole plus a meticulous study of curettings obtained *at the time of the molar evacuation*, there will be a more accurate pathologico-clinical correlation in these clinically malignant varieties. There is a suggestion, in our admittedly small series of chorioncarcinomas, that some areas of the original mole and/or the curettings resemble the ultimate metastasis. This was not invariably so, as has been mentioned before. Curettings done some weeks or months later may be of no help in evaluating either of these serious types of chorionic malignancies, since the primary tumor may have disappeared, metastasized, or buried itself in the uterus.

The lack of a specific pathologico-clinical correlation in any given case of hydatidiform mole is shown by the decreasing, yet definite percentage of patients having a benign clinical course, even in those moles diagnosed as probably (Group V) and definitely malignant (Group VI). That these clinically benign cases of hydatidiform mole, irrespective of their original molar group, are truly cured is shown by the high proportion of subsequent pregnancies: 49.6 per cent in the 147 patients for the first five groups. (Even two of the 53 patients showing some evidence of uterine invasion became subsequently pregnant, both in the chorionepithelioma in situ group. The latter patients, as a whole, had an excellent prognosis, as did those patients showing syncytial



endometritis.) Aside from the evidence of absolute cure, as shown by subsequent pregnancy, the probable cure rate in the clinically benign patients in the first five groups is significant: 36 out of 147 (24.6 per cent) alive and well two or more years following the mole. The possible cure rate in this group of patients is 18.3 per cent, or 27 out of 147 living and well less than two years. The remaining 11 patients (7.5 per cent) are the only ones in the clinically benign series of 147 on whom we have no follow-up. (They likewise constitute the only ones of the entire series of 200, or 5.5 per cent, on whom we have no evidence of what happened to the patient following her molar pregnancy. This is based on the reasoning that a subsequent hysterectomy—even though that patient subsequently had no follow-up—constitutes some degree of follow-up.) Thus, the combined prognostic or cure rate in these clinically benign series may be as high as 92.5 per cent.

The follow-up data on the histologically and/or clinically malignant moles may be summarized by the general statement that all cases except those of chorioncarcinoma have an excellent prognosis—even the chorionadenoma destruens. The latter is true only if such cases have a hysterectomy, because such tumors may kill by perforation, sepsis, or hemorrhage. Since these locally invasive but nonmetastasizing choriomas have a minimum probable cure rate of 78 per cent, or 25 out of 32 cases living and well two or more years after hysterectomy, it is apparent that they are not in danger of dying from subsequent metastases. That the probable cure rate is much higher—even 100 per cent—is indicated from the fact that none of the cases in this category have ended fatally, except the one patient who died of peritonitis five days postoperatively. Our lack of follow-up data on all 32 cases makes it impossible to say what happened to all of the cases. However, it would seem logical to assume that if any of these cases tend to have metastases, some of the 21 on whom we do have adequate follow-up data would have done so within two years after the molar pregnancy.

The probability that none of the chorionadenoma destruens are subject to metastasis appears to be of clinical significance. They form the largest single group who develop clinical malignancy, the 32 cases constituting 16 per cent of the entire series of 200 moles, as against the five cases of chorioncarcinoma which constitute only 2.5 per cent of the series. Since the former group can be benefited by proper therapy (hysterectomy), while the former probably cannot be benefited by any therapy, it behooves the clinician to be on the watch for evidence of a chorionadenoma destruens. All of our cases (except one who had only a persistent positive A-Z test) on whom we have adequate information, showed subinvolution of the uterus accompanied by bleeding. These occurred on an average within 35 days following the passage of the mole, although the extreme variations were five to one hundred twenty-six days in 19 cases. Four cases with immediate hysterectomy are excluded for obvious reasons in discussing the possibility of subinvolution and postpartum bleeding. The eight remaining cases in the series have insufficient data on which to draw any conclusions as to time or reason for hysterectomy.

In only one of the 32 cases (referred to above) was the uterus removed solely because of a persistently positive Friedman test (two and four weeks post partum). Since the test for chorionic gonadotropic hormone may remain positive for as long as sixteen weeks following the expulsion of a benign mole (Toland<sup>19</sup>), the average being three months, with variations of six days to ten months according to Payne,<sup>16</sup> it is obvious that it is of little help in diagnosing chorionadenoma destruens. However, postmolar vaginal bleeding and subinvolution of the uterus are almost invariably present, and indicate the need for at least a uterine curettage, with the probability of a subsequent hysterectomy. Curettage in this series of chorionadenoma destruens was often done, showing that the operation per se does not increase the danger of subsequent metastasis.

### Summary

In view of the proved curability, all grades of chorionic malignancy except chorioncarcinoma, regardless of how the latter is treated, it seems reasonable to adopt a conservative attitude regarding the pathologico-clinical approach to the problem of hydatidiform moles. An adequate pathologic examination of molar tissue *and curettings, done at the time of operation*, is valuable but not of absolute diagnostic or prognostic significance. The more malignant the mole appears morphologically, the more likely the patient is to develop some form of chorioma. Therefore, the clinician should be apprehensive regarding clinical malignancy in proportion to the degree of apparent pathologic malignancy. Such clinical malignancy (except in some chorioncarcinomas) is usually indicated by subinvolution of the uterus and bleeding, which indicates the need for a repeat curettage and probable hysterectomy. Chorionic gonadotropic hormone tests are of little or equivocal value during the period when treatable clinical malignancies are first developing, i.e., on an average thirty-five days after the expulsion of the mole. By thus adopting a conservative attitude of "scientific apprehensive expectancy" (courtesy of Dr. F. C. Irving) many uteri will be saved that are now needlessly removed without adding appreciably—if any—to the death rate from chorionic malignancy.

### Conclusions

1. A series of 200 hydatidiform moles, gathered consecutively over a period of eleven years from 109 medical communities in the eastern half of the United States, have been examined.
2. Follow-up data on 94.5 per cent of all patients are available.
3. Microscopic criteria of six groups of hydatidiform moles have been described and illustrated. These show a marked, but not an absolute correlation between the degree of apparent molar malignancy and the tendency of the patient to develop some grade of chorionic malignancy.
4. In 73.5 per cent of the entire series there was no subsequent development of either pathologic or clinical malignancy, as judged from the follow-up data available on 90.5 per cent of this particular group.



5. In 26.5 per cent of the entire series, the various grades of chorionic malignancies occurred as follows:

a. Chorionepithelioma in situ	3.5 per cent
b. Synechtial endometritis	4.5 per cent
c. Chorionadenoma destruens	16.0 per cent
d. Chorionecarcinoma	2.5 per cent

6. The prognosis of all grades of chorionic malignancy is excellent, except for the relatively uncommon, invariably fatal chorionecarcinoma, as judged from the follow-up data available on 89 per cent of this entire malignant group.

7. In the first three grades of chorionic malignancy, all curable if properly treated, clinical evidence of malignancy is usually shown by continued postmolar vaginal bleeding and/or subinvolution of the uterus.

8. A policy of clinical watchful waiting may be followed until such objective evidence of malignancy develops without increasing the danger to the patient from chorionic metastasis.

9. Such individualized clinical conservatism will thus save many uteri that might otherwise be needlessly sacrificed in haste merely because the patient has passed a hydatidiform mole.

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### Discussion

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—I am impressed with the industry with which this material has been collected, the care and diligence of its study, and the logical effort the essayist has made to evaluate his findings.

The difficulties and problems in this field are many; Dr. Hertig has mentioned a few of them:

(1) The difficulty of securing representative and significant materials for study—the surgeon submitting the gross material evacuated, but often failing to submit separately the curettings of tissue which was in direct contiguity with the uterine wall. The latter, of course, is extremely important in an evaluation of the malignant propensities of the growth.

(2) The variable nature of growth activity in molar tissue, and the difficulty of “pigeonholing” lesions. In this direction the Ewing classification of malignant types seems cumbersome and not too meaningful, for each mole differs from another in structural appearance and biologic behavior.

(3) The tendency of these tumors to follow in their behavior their trophoblastic prototypes makes prognostication uncertain.

(4) In view of these several considerations, the establishment of standards of malignancy is in this field especially difficult—anaplasia, pleomorphism, invasion, portability, persistence at placental site, and ultimate lysis in all situations being features not only of “malignant” mole, but also of physiologically and embryonically normal syneytium.

The very skeptical may say that the only sure proof of malignancy in mole is the autopsy finding in the dead patient, and point to the fact that of the 117 patients in Hertig's Group IV, V, and VI, only 47 were proved to have malignancy, even upon the conditions which he has set forth. This statement in no way detracts from the importance of the paper, but points simply again to the intricate nature of this problem, and indicates that the pathologist is still going to be unable, oftentimes, to give us an absolute yes or no to the malignancy of molar tissue.

What Dr. Hertig has set out to do, and what he has accomplished as far as seems humanly possible, is to set up groups of cases within which the similarity of histologic findings indicates that malignant manifestations may be anticipated in a rather uniform percentage of cases. Then he who rides may read.

This matter is important both to the pathologist and the clinician. To the pathologist seeing only occasional material, it provides a standard for histologic comparison. To the clinician it provides something more than silver-ball conjecture as to what the prospects of his case may be. I surmise that Dr. Hertig had no further purpose than this in mind and, like all real students of his subject, he is content to add to our knowledge these few important observations.

In conclusion, I would say that this contribution has “squeezed the orange dry” as far as histologic study of hydatidiform mole is concerned, and that further progress in this field will have to wait upon the studies of the biologist and enzyme chemist who may ultimately tell us why in some instances the mole destroys the host and in others the host dissolves and eliminates some of even the most malignant-appearing moles.

DR. ROBERT A. ROSS, Durham, N. C.—The essayist, by painstaking study of specimens and careful follow-up of patients, has been able to predict malignancy in very high percentage of instances and, with known methods of treatment, should favorably influence the mortality from the malignant chorionic tumors. The fact that it appears impossible, from examination of the mole itself, to state the definite malignancy that the mole will ultimately exhibit is not so noteworthy as is the correlation between the microscopic appearance of a mole and evidence of malignancy in the uterus. We know that this bizarre tumor manifests itself in varying degrees of malignancy, extension, progress, and prognosis, yet by prompt, judicious surgery and deep x-ray therapy we can promise relief, with the exception of those who have chorioncarcinoma, to the majority of these patients.

This report also substantiates the observations of most men regarding such studies; the highly malignant carcinoma is relatively rare. Thus the essayist has satisfactorily dealt with the hydatidiform mole and the malignancy that often follows. However, we know that at least one-half of these malignant tumors follow other types of pregnancy or pregnancy complications. Diseases of the chorion are common, but hydatidiform mole is rare. When the uterus and associated mechanism of defense cannot destroy chorionic tissue, one should immediately be alert to the possibility of chorionic malignancy. This inability to prevent chorionic sustenance and growth is evidenced by abnormal bleeding

and the histologic appearance of tissue as described. In the study of the autopsy material in our patients, who did not have a history of previous hydatidiform mole, we noted a difference in the degree of malignancy and appearance between the cells in the uterus and the cells in the lungs. In one patient with tubal pregnancy, the malignancy was found only on careful recheck of the material after x-rays of the lungs were suggestive of metastases.

If our understanding of the histology and hormonology of these tumors is correct, it is difficult to explain a negative chorionic gonadotropin assay, except it be due to faulty animals, specimens, or technique.

It is generally agreed that assays for chorionic gonadotropin are of very definite value in diagnosing and following cases of hydatidiform mole and chorionepithelioma.

A negative qualitative test in the face of frank evidence of a mole or following removal of malignant chorionic tissue, conveys to the investigator not only a sense of relief, but also one of doubt. An initial negative test should be checked immediately and, if still negative, tests should be repeated at frequent intervals. The frequency and duration of this repetition should be governed by clinical evidence.

Positive qualitative tests also may be viewed with suspicion under certain circumstances. If the more common causes of excessive gonadotropin production in women can be ruled out, one probably is justified in assuming a state of emergency exists in instances where the presence of a mole is suspected or in which there is reason to believe a mole has been passed. If a positive test can be correlated with factual evidence of a mole, there should be no hesitancy about institution of immediate measures.

Positive qualitative tests obtained with spinal fluid still are considered of positive diagnostic import. We find, however, that a negative test obtained with spinal fluid is not always of diagnostic value.

Quantitative assays for chorionic gonadotropin need be done only following detection of this substance by qualitative tests.

We have come to realize that it may be unfortunate to place great emphasis, as regards diagnosis, on the so-called "large amounts" of chorionic gonadotropin excreted in instances of malignant moles and chorionepithelioma. It has been shown on a number of occasions that the values of gonadotropin excretion in some cases are very much lower, and often no greater, than those found during a corresponding period of normal pregnancy.

When clinical manifestations indicate investigation of a pregnancy that has progressed beyond ninety days, and if maintained or increasing gonadotropin levels are found, then the presence of a mole or chorionic malignancy should be ruled out. If the pregnancy had advanced into the last trimester, a diagnosis might have to be made between toxemia of pregnancy and chorionic cancer.

During the past 15 years at Duke University we have treated seven patients with diagnosed hydatidiform mole and five patients with diagnosed chorionepithelioma, and have studied tissue from 12 additional patients. None of the malignancies followed moles, and none of the seven patients with mole, on whom we have adequate follow-up data, has developed chorionepithelioma, though one classed as doubtful, who refused operation, had intermittent bleeding and positive chorion gonadotropin tests for a year. Three had subsequent pregnancies. One malignancy followed a tubal pregnancy. The elapsed time from the last pregnancy until diagnosis of chorionepithelioma varied from two months to four years, with death in two months to three years.

It is hoped that the essayist's presentations will lead to a clearer understanding of the malignancy potentialities of the mole and a better classification of the chorion malignancies. Perhaps the use of three groups for the hydatidiform mole and designating the malignancies by grades, such as the adenomas and carcinomas of other groups, would lead to clarifications and unanimity. The advantage of a repository for such malignant tumors is suggested.

DR. EMIL NOVAK, Baltimore, Md.—It is because I am afraid that Dr. Hertig's paper may exert a harmful influence that I feel impelled to express disagreement with some of his observations. In the first place, he places 53 of his 200 cases of mole in the

malignant group, a startling proportion. This statement in itself might well lead some to more radical treatment of hydatidiform mole than is actually justified. Many years ago I reported a series of, I believe, 11 moles, all treated by simple evacuation of the uterus, and none developing any manifestations of malignancy. At the same meeting, the late J. Whitridge Williams and J. B. DeLee reported even larger groups, with the same conservative therapy and the same absence of unpleasant sequelae. The seven cases in Dr. Hertig's series which terminated fatally were obviously chorionepitheliomas, and the slides of the two or three cases of this group which he threw on the screen showed this very clearly.

But in his 53 malignant cases, Dr. Hertig has included many which he apparently puts into this group on the basis of a histologic evaluation which, I think, is fallacious. I have seen any number of moles with just as much trophoblastic proliferation and just as much evidence of what he calls anaplasia, in which the clinical course was entirely benign. Anaplastic activity is far more difficult to establish in trophoblast than in ordinary epithelial or connective tissue elements. Huge hyperchromatic nuclei are common even in normal trophoblast, and so is destructiveness and invasiveness, and so is the physiologic form of metastasis which we call deportation of villi or trophoblast.

After all, chorionepithelioma is an exceedingly rare disease, and in some very large clinics not a single case has been observed. Benign hydatidiform mole is far more common, and I personally do not believe that much more than 1 per cent of moles become actually malignant, though a wrong diagnosis to this effect has a much higher incidence. To lay down such histologic criteria of malignancy as does Dr. Hertig is not justified unless it can be supported by clinical evidence, which in the malignant choriomas usually means the death of the patient.

There is usually no great difficulty in the microscopic diagnosis of the frankly benign or the frankly malignant cases, but there is a small group in which pathologists will differ, and to which such terms are applied as malignant mole or chorionadenoma destruens, although I think the latter designation, suggested by Ewing, a very poorly selected one. This group, characterized clinically by a lower degree of malignancy, and especially by extensive intravascular penetration, seems to me to bear the same relation to chorionepithelioma as does an adenocarcinoma of Grade I to one of Grade III or IV. In other words, one encounters all gradations of benign or malignant neoplastic activity in the chorionic epithelium as on any skin or mucous membrane surface. The simplest concept is that of two groups, the benign and the malignant chorioma, although in this field, as in all others in pathology, there is a small borderline group, of suspicious or slight malignancy, in which there is bound to be difficulty in microscopic interpretation.

Finally, and it seems to me rather paradoxically, in view of what he has presented to us in his paper, Dr. Hertig advises a conservative plan of management of hydatidiform mole, with which most of us will fully agree.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Management of this interesting problem resolves itself into two objectives: the diagnosis and removal of malignant chorionic tissue while it remains localized in the pelvis, and the avoidance of unnecessary surgery during the childbearing age because of the fear that malignant chorionic tissue might be present.

In the past, only two approaches to this problem were available: first, the clinical picture of each case, and second, the microscopic traits of tissue that was removed or expelled. Recently, a third approach, hormone studies, have proved to be of such great value that they are considered by some to be the most important of the diagnostic procedures.

Dr. Hertig's work will prove to be a valuable contribution to the subject of mole and chorionepithelioma, and his stand is to be admired, particularly in view of the great hesitation that has been voiced by numerous eminent pathologists, including Pick, Frank, and Novak, who have pointed out the marked difficulty that attends the attempt to evaluate the malignant properties of chorionic tissue by means of microscopic examination. Because of this difficulty, the diagnostic possibilities of hormone analysis were eagerly seized upon by students of the subject.

Since the production of chorionic hormone is one of the properties of chorionic tissue, whether normal or abnormal, the body fluids of a person harboring such tissue would be expected to contain demonstrable quantities of this secretion. This expectation has been confirmed and has been attested by many investigators during the last ten or fifteen years. Quantitative assays of the chorionic hormone have proved to be invaluable as an aid in the early diagnosis of hydatidiform mole. Following removal or expulsion of the mole, except in rare instances, regularly spaced hormone titration of the blood serum has been shown to permit differentiation between recovery and the development of chorionepithelioma. On one hand, a gradual decrease, or the lack of an increase, in the chorionic hormone—even over an extended period of observation—indicates the absence of chorionepithelioma. On the other hand, an increase in the prolactin values denotes the presence of a malignant process or of an intervening pregnancy. The latter condition may be proved or disproved by such assays, for the characteristic hormone peak of early pregnancy does not occur in the presence of chorionepithelioma. The hormonologic identification of chorionic malignancy rests not upon a single quantitative or qualitative determination, but upon the demonstration of increased values by means of repeated assays. Deliberate consideration of the clinical, the microscopic, and the hormone picture of each such problem will permit the effective separation of those who require radical treatment from those for whom such treatment would consist of needless mutilation.

DR. HERTIG (Closing).—In answer to Dr. Novak's question regarding the high proportion of malignancies in this series, namely, 53 out of 200 cases, it must be emphasized that such malignancies included various grades of histologic and/or clinical malignancy. Thus, there were seven cases we called chorionepithelioma in situ, two of the women subsequently had babies, while the remaining five were living and well either with or without their uteri one and one-half to five and one-half years later. The nine cases whose uteri showed syncytial endometritis, a pathologic entity recognized by the late James Ewing, all ran a clinically benign course, except the one patient dying postoperatively of sepsis. The 32 cases of chorionadenoma destruens, or locally invasive mole, likewise ran a clinically benign course, although it is recognized that such a condition may ultimately kill the patient by uterine perforation, sepsis, or hemorrhage, even though there is no clinical evidence of metastasis. There remain only five cases of chorioncarcinoma, about which there can be no argument as to their ultimate malignancy, since all died of metastases within two years. Since it is apparent that there are various histologic and/or clinical grades of chorionic malignancy, it becomes imperative to distinguish between them, rather than to designate them all as chorionepithelioma.

Dr. Payne's question regarding the value of hormone tests with respect to the diagnosis of chorionic malignancy following a mole is well taken. Perhaps I did not make this matter clear, but what I endeavored to point out, based on Dr. Payne's own data, was that during the first month after evacuation of a mole, the qualitative chorionic gonadotropic hormone tests were of equivocal value because they remain positive, on an average, three months following a benign mole, with variations of six days to ten months. Since this interval coincides roughly with the average postmolar period of thirty-five days during which treatable forms of chorionic malignancy show uterine bleeding and/or subinvolution, it is better to rely on such clinical criteria rather than qualitative hormone tests alone in determining whether a uterus should be removed. Quantitative hormone tests, however, are of great value in evaluating the period following molar evacuation, since they usually show not only the presence of viable trophoblast, but whether it is increasing or decreasing in amount.

In conclusion, I wish to emphasize that the treatment of a patient harboring a hydatidiform mole should be individualized, and that this often difficult problem needs all the hormonal, clinical, and pathologic data obtainable for its solution.

## CONGENITAL MALFORMATIONS ASSOCIATED WITH DEVELOPMENTAL DEFECTS OF THE FEMALE REPRODUCTIVE ORGANS\*

LAWRENCE R. WHARTON, M.D., BALTIMORE, MD.

THE study of congenital defects of the genitourinary system has been facilitated in recent years by developments in intravenous urography, endocrinology, and embryology. Interest in these malformations has been increased by the evolution of new operative measures, by which some of them may be corrected or ameliorated. With this in view, it seemed worth while to survey the subject of congenital malformations of the female reproductive organs, especially with respect to the associated developmental defects.

I shall consider first, congenital malformations of the ovary, especially agenesis of the follicular epithelium, a condition recently described by both European and American observers. In America, this condition has been studied particularly by Albright and his associates,<sup>12</sup> and Wilkins and Fleischmann.<sup>7, 12</sup> We shall then consider the various malformations due to faulty development of the Müllerian ducts and the cloaca.

### Agenesis of the Ovarian Follicular Epithelium

*Pathology:* The term "ovarian failure" has been used for years in gynecologic and endocrinologic parlance. In the past, it has generally been assumed that ovarian failure was secondary to some endocrine disorder, marked by a lack of normal gonadotropic stimulation of the ovaries and subsequent absence of function, or disordered function, of the ovaries. Although this is undoubtedly the explanation of many cases of ovarian dysfunction, Albright and Wilkins and Fleischmann<sup>7, 12</sup> have isolated from this heterogeneous group one syndrome in which this explanation does not hold. In this group, they have found that the ovarian failure is due to agenesis and lack of follicular epithelium; the ovary is hence quite incapable of function, regardless of the efficiency of the gonadotropic hormones.

The characteristic feature of this condition is the rudimentary development of the ovaries and the complete absence of any ovarian follicular epithelium (Fig. 1).

The microscopic appearance of the ovary in agenesis of follicular epithelium is shown in Fig. 2. Serial sections of one ovary of this young woman failed to show any trace of ovarian follicles.

In these cases, the absence of any follicular activity produces characteristic sequelae. The uterus, Fallopian tubes, vagina, external genitals, and breasts remain undeveloped. The condition of the uterus and Fallopian tubes is shown in Fig. 1. Pubic and axillary hair may be present, due to the activity of the androgens (Albright).

*Clinical features:* The essential gynecologic characteristics are the lack of development of the reproductive organs and breasts, amenorrhea, and lack of function of the ovaries. In contrast with this, the function of all of the other endocrine glands is normal. The level of the follicle stimulating hormone (F. S. H.) is high, as it is after castration or the menopause; the 17-ketosteroids are low.

\*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

These findings, together with the pathologic histology of the ovaries, clearly distinguish these cases from ovarian dysfunction due to disorders of other endocrine glands in conditions such as Froehlich's or Cushing's syndromes, or cretinism.

In 1944, Wilkins and Fleischmann reported three such cases, proved by histologic examination of the ovaries. These cases were identical with the syndrome previously reported by Albright and his associates without pathologic proof. They also were identical with cases that had been reported by German observers, some of which had been proved histologically. In 1946, Wilkins and Fleischmann reported that they had seen 13 such cases. This makes a total of about 50 cases of agenesis of the ovarian follicular epithelium that have so far been reported in the literature. From this, one would judge that the condition is not extremely rare.

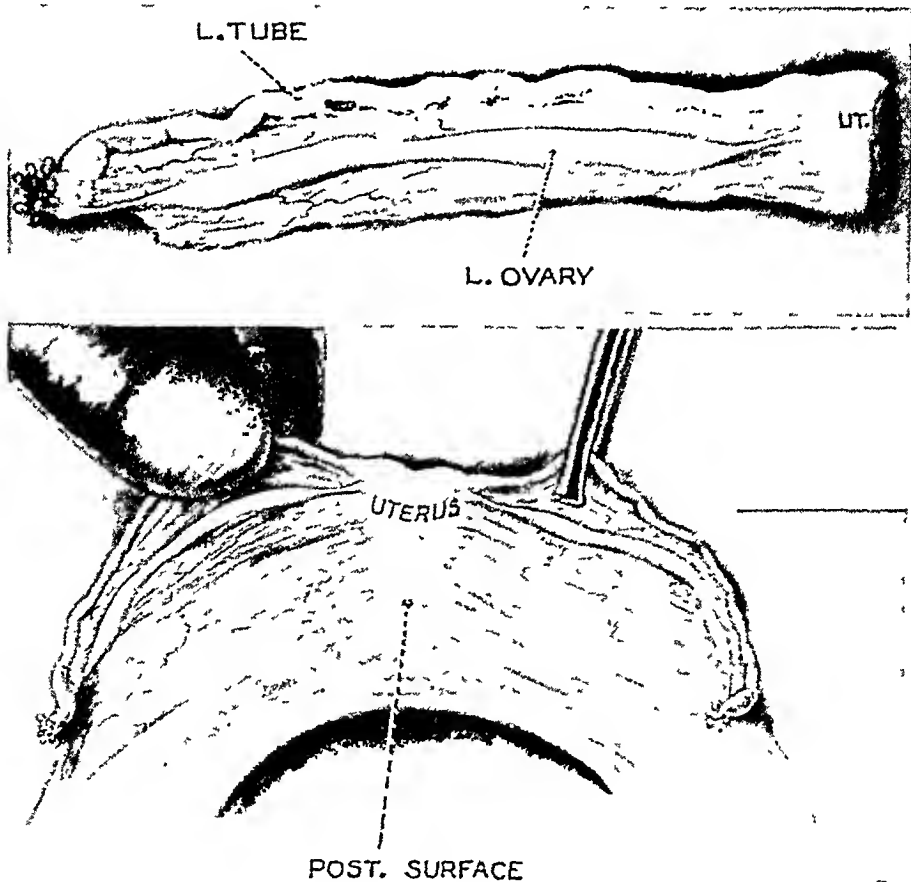


Fig. 1.—Agenesis of follicular epithelium of ovary in a young woman almost 18 years of age. The reproductive organs are rudimentary. The Fallopian tubes are hardly more than threads. The uterus measures 3 cm. long and 1 cm. in diameter. Each ovary is an elongated ridge of white tissue, 3 mm. in diameter, about  $2\frac{1}{2}$  cm. long. (From Wilkins and Fleischmann, *J. Clin. Endocrinol.* 4: 357, 1944.)

As a matter of clinical observation, I wonder whether there are not also instances of partial agenesis, as well as complete lack of ovarian follicular epithelium—in other words, in which the number of ovarian follicles is decreased, but not altogether lacking. Possibly this may be the explanation for some cases of marked oligomenorrhea, in which the patient menstruates only once or twice a year. Some of these women have no other endocrine disorder, and bear children. In some instances, furthermore, the oligomenorrhea is clearly a familial characteristic, shared both by mother and daughters. This would again suggest the



genetic, or hereditary, nature of the disturbance. If this explanation is tenable, it explains the futility of gonadotropic therapy in such situations.

*Malformations associated with agenesis of the follicular epithelium:* The genetic nature of the condition is further attested by the associated congenital anomalies. In the 32 cases first collected and reported by Wilkins and Fleischmann, they listed the following associated malformations: retardation of the growth resulting in short stature, coarctation of the aorta, webbed neck, defects of the eye, congenital deafness, spina bifida, and mental retardation. These were probably entirely independent genetic faults, indicating the widespread defectiveness of the germ plasm. There were also occasional acquired defects, such as osteoporosis, which was probably due to the ovarian insufficiency, and also hypertension, the cause of which was not always clear.

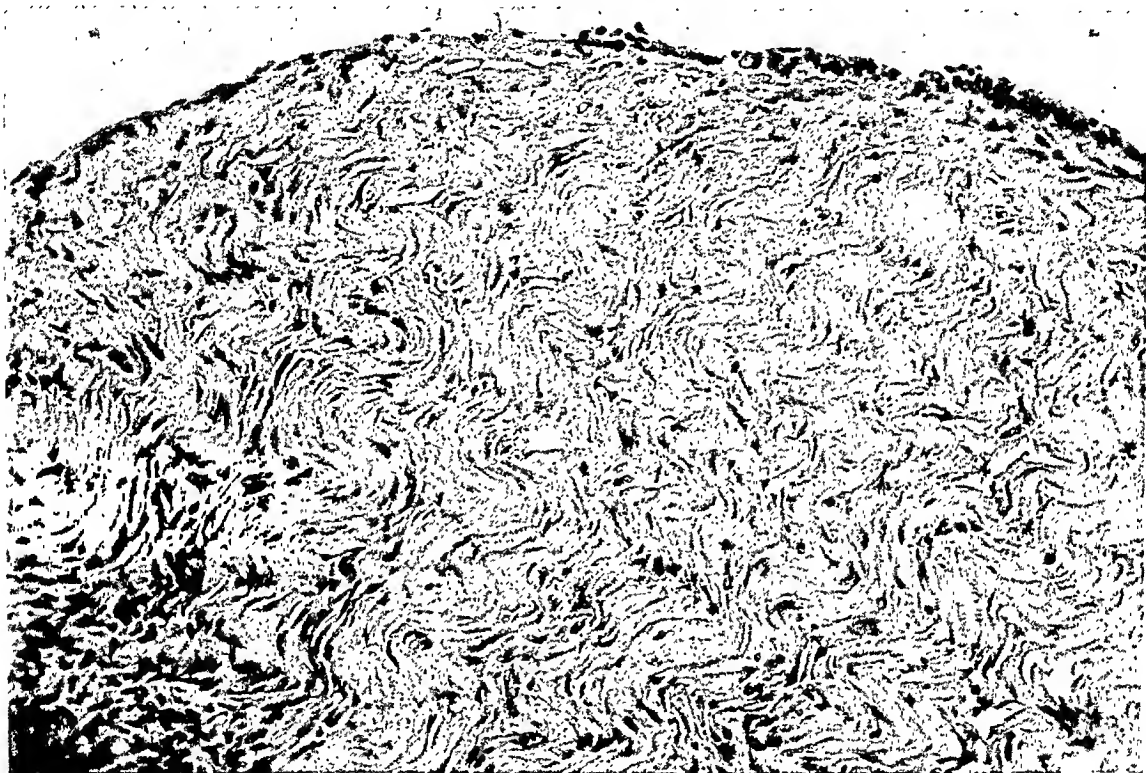


Fig. 2.—Cross section of ovary shown in Fig. 1. The ovarian stroma is normal, but there are absolutely no ovarian follicles. (From Wilkins and Fleischmann: *J. Clin. Endocrinol.* 4: 357, 1944) ( $\times 250$ .)

This ensemble of congenital malformations found in cases of agenesis of the follicular epithelium indicates that the genetic fault is general, and not limited to the urogenital fold. This distinguishes it from malformations of the Müllerian ducts, in which the defects are usually confined to the urogenital fold. The significance of this will be discussed later.

### **Congenital Anomalies of the Müllerian Ducts and Associated Malformations**

The next group includes cases in which the chief lesion in the reproductive organs is in the Müllerian ducts. In some instances, the associated lesions are more important than the defect in the reproductive organs. In this group, we are merely citing a few typical defects, illustrating the embryologic associations as we have found them.

*Bicornate uterus; associated lesions, extrophy of the bladder; separation of symphysis pubis.*—The patient was a woman 36 years old, who complained of an extrophy of the bladder. The usual picture was present, the bladder being



entirely exposed on the anterior abdominal wall, the anterior bladder wall being absent, the ureters opening externally and causing a continual leakage of urine on the anterior abdominal wall. The symphysis pubis was separated widely. The left ureter and kidney were normal; the right ureter and kidney pelvis were widely dilated, forming a hydronephrotic mass in the right flank, which secreted only a trace of diorast in sixty minutes.

The lesion in the reproductive organs consisted of a bicornate uterus.

The treatment in this case consisted of implantation of both ureters into the rectosigmoid, performed in 1942. This eliminated the urinary incontinence, and enabled the skin to cover the bladder almost completely. The bicornate uterus was causing no symptoms, and was not disturbed.



Fig. 3.—Absence of uterus and vagina, associated with crossed unfused ectopy of left kidney.

*Absence of uterus; associated lesion; crossed unfused ectopy of left kidney.*—Miss J. W., a 21-year-old college student, had complete absence of the vagina and uterus, due to nonunion of the Müllerian ducts. The urinary lesion consisted of crossed, unfused ectopy of the left kidney. The urethra and bladder were normal. The ureteral orifices and trigone were normal. The right ureter followed its usual course to the right kidney, which was normal in every particular. The left ureter crossed the pelvis in front of the sacral promontory and led to a low left kidney which was situated below the right kidney in the right flank, and seemed to be completely separate from it. This is a rather rare urinary malformation (Fig. 3).

The treatment in this case was construction of the vagina. The urinary situation was causing no symptoms, and was not disturbed.

*Absence of vagina and uterus; absence of right kidney; ectopic right ovary.*—Miss B., a young woman 21 years old, was seen in the Women's Hospital in 1940. She had no vagina and no uterus. She was admitted to the hospital be-

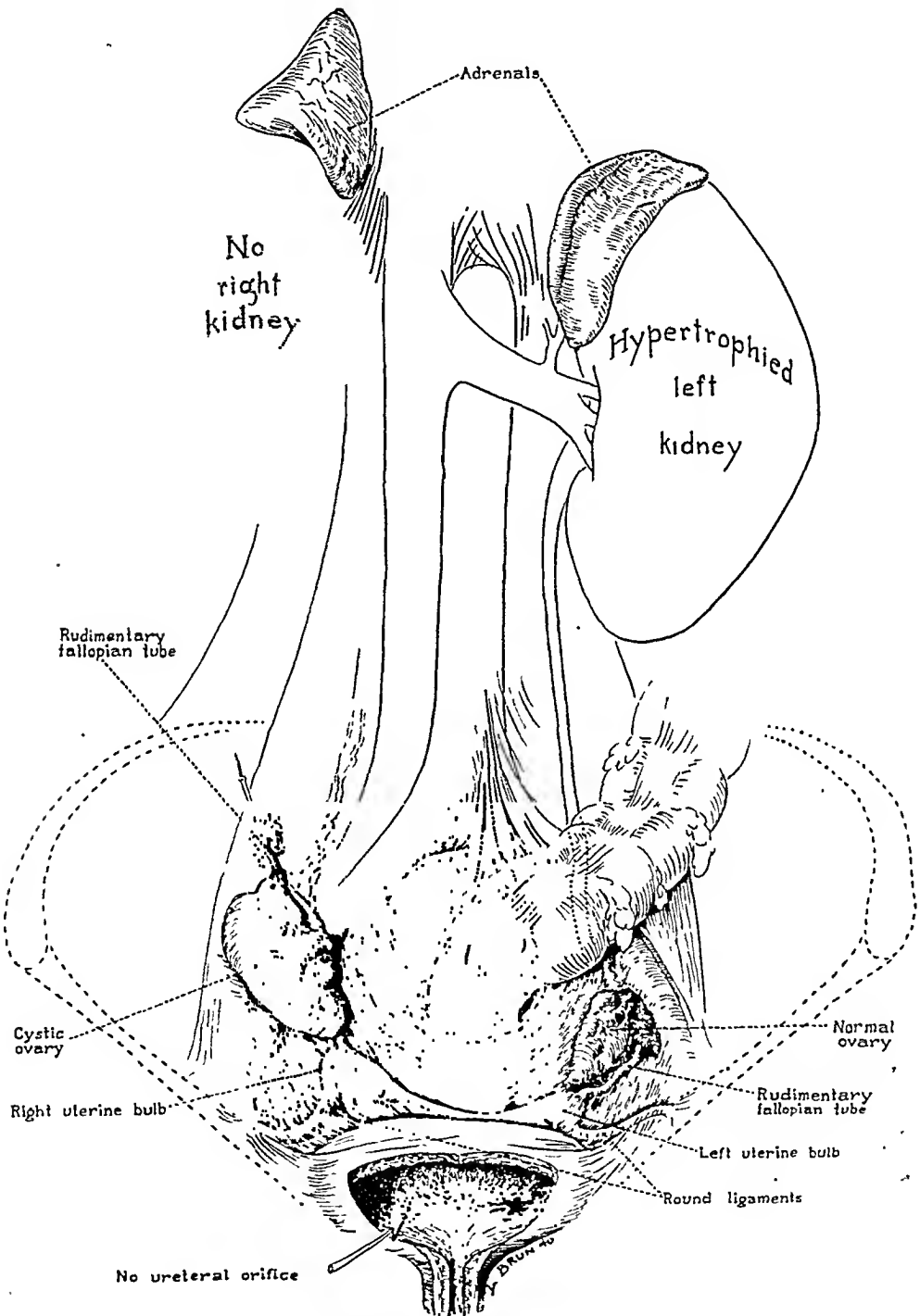


Fig. 4.—Absence of vagina and uterus, associated with agenesis of right kidney and ectopic right ovary. (From L. R. Wharton, *Gynecology, Including Female Urology*, Philadelphia, 1943, W. B. Saunders Co.)

cause of recurrent appendicitis as a patient of Dr. Allen Deekert. The condition of the genitourinary organs is shown in Fig. 4. The right kidney and ureter were completely absent. The right ovary was enlarged, ectopic, lying in the right iliac fossa. It was cystic. The Müllerian ducts presented the typical

picture seen in these lesions. The Fallopian tubes were present, rather rudimentary, with patulous fimbriae. Their mesial ends were separated from each other by a space of about 5 cm., ending in small bulbs. There was no vagina.

The treatment was appendectomy; the patient did not wish to have a vagina constructed.

*Absence of vagina and uterus; absence of right kidney; solitary left ectopic kidney in sacral hollow; bilateral undescended ovary; dermoid cyst of right ovary; papillary cystadenoma of left ovary; situs transversus of large intestine.*—Miss L. B., aged 23 years, was a clerk for the Federal Government. Her general health had been excellent. Except for the amenorrhea, the first symptom had been a palpable abdominal mass, first noted by the patient herself in 1940,



Fig. 5.—Absence of vagina and uterus, associated with absence of right kidney; solitary kidney, left, ectopic, in sacral hollow; bilateral undescended ovary; dermoid cyst, right ovary, papillary cystadenoma, left ovary; situs transversus, large intestine.

when she was 17 years old. At that time, she was admitted to a hospital in Pineville, La., where the ovarian masses and the appendix were removed. The right ovary contained a dermoid cyst 6 cm. in diameter; arising from the left ovary was a papillary cystadenoma 14 cm. in diameter. The sigmoid and descending colon lay in the right half of the abdomen, and the appendix and ileocecal valve in the right upper quadrant. At that operation, the procedures were bilateral oophorectomy and appendectomy.

After this, three unsuccessful attempts were made to construct the vagina. Fig. 5 shows the location of the solitary ectopic kidney. The ureter swings a little to the left as it crosses the cul-de-sac of Douglas. The surgical treatment was construction of the vagina. In this vaginal dissection, there was no plane of cleavage, and almost every centimeter of space had to be cut by sharp dissection to separate the rectal and bladder walls. Also, the location of the ureter gave us some concern as our dissection approached the cul-de-sac of Douglas. The vagina was lined by Thiersch grafts, all of which were successful. The result of the plastic operation was excellent.



Fig. 6.—Solitary ectopic kidney in a young woman 21 years of age, with absence of vagina and uterus.

*Absence of vagina and uterus; absence of left kidney; solitary ectopic right kidney.*—Miss J. L., aged 21 years, was operated upon, apparently for "appendicitis," in 1942. She had had recurring monthly pain in the lower abdomen, especially in the right iliac fossa. At operation, the congenital malformation was discovered—absence of uterus and vagina. Her amenorrhea had been attributed to an imperforate hymen. Also, at this operation, the solitary ectopic kidney was discovered.

In May, 1946, she was admitted to the Women's Clinic, and was referred to me by Dr. TeLinde. The gynecologic anomaly had begun to make an introvert out of the young woman. Physically, she was perfectly normal, except for the anomalies in the genitourinary system. The breasts, secondary sex

features, and external genitals were normal. The vagina was represented by a depression 2 cm. deep. Fig. 6 shows the solitary ectopic right kidney, lying in the sacral hollow, with the calyces pointed toward the right iliac fossa. The right ureteropelvic junction is a little to the left of the midline, just above the coccyx, and then crosses the pelvic floor to reach the right half of the bladder. Cystoscopy showed the left ureteral mound and left ureteral orifice to be absent; the right ureteral orifice was normally situated and functioning normally.

At operation (May 21, 1946) a vagina was constructed, using our technique and Thiersch grafts.

*Absence of vagina and uterus; horseshoe kidney.*—This patient was seen several years ago, and a vagina was successfully made. Unfortunately, the roentgen films were destroyed in accordance with the regulations of the Fire Department.

*Vulvovaginal anus with malformation of right kidney and ureter.*—Mrs. L., 32 years of age, complained of habitual abortion. She had four pregnancies, none of which she carried beyond the third month.

The author first saw this patient ten years ago, when she complained of rectal incontinence. This was due to the vulvovaginal anus, the anal orifice being situated just within the vaginal orifice. There was no sphincter around the vaginal opening of the rectum, and the patient was completely incontinent, except when constipated. The reproductive and intestinal tracts were otherwise normal.

A routine urologic study revealed the very rare anomaly shown in Fig. 7. Repeated urograms have failed to show the exact extent of division of the upper urinary tract. The kidney pelvis is divided completely into at least two, and probably three or four parts.

## Discussion

*Agensis of Ovarian Follicular Epithelium.*—We have already mentioned the pathologic features of the ovary in this disorder, and have listed the genetic faults that have been found associated with it. In addition, this condition suggests several other considerations, among which are the *origin of the germ cells*, the *nature of the genetic fault*, and the *bearing of this condition on the differentiation of sex*.

*Ovarian Agensis and the Origin of Germ Cells.*—These cases possibly have some bearing on theories concerning the origin of germ cells. According to one theory, the germ cells originate in the urogenital fold along with the stroma of the ovary, the Müllerian ducts, and the Wolffian bodies and ducts. According to another theory, they have a much earlier origin in the yolk sac, whence they migrate at an early date to the urogenital fold. There they collect to form the sex cells of the gonad. In the forthcoming number of the *Contributions to Embryology*, Witschi traces the migration of the germ cells to their ultimate home in the gonadal folds.

The cases of ovarian agensis, which we have just described, seem to lend support to the second theory recently espoused by Witschi. In these cases, there is a complete agensis of the follicular epithelium of the ovary, without any other malformation of the genitourinary organs. In the 40 or 50 cases reported in the literature, Wilkins and Fleischmann<sup>7, 12</sup> have yet to note an instance of double uterus, absence of the vagina, or ectopic kidney, lesions which are commonly associated in congenital defects of the urogenital folds. The absence of

such associated urogenital malformations would therefore suggest that the genetic fault lies elsewhere, probably in primordia of the germ cells, and is effective before they migrate to the gonadal folds. Corner<sup>13</sup> shares this opinion with the author. This would suggest that the germ cells do not originate in the urogenital folds.

*The Nature of the Genetic Fault in Absence of Follicular Epithelium.*—The malformations associated with this syndrome are so diverse that it is impossible to suppose that they are the result of a fault localized in a single primordium.



Fig. 7.—Vulvovaginal anus with ectopic divided right kidney, and divided ureter. There are at least two, and probably four divisions of this kidney.

This distinguishes the syndrome basically from the simpler defects of the urogenital fold, which are not very frequently accompanied by remote malformations. It also supports the views expressed years ago by Nagel, Guizzetti, Pariset and others, that congenital faults of the ovaries are likely to be associated with extensive general genetic deformities. The only explanation of such fundamental and widely scattered anomalies is that the germ plasma is generally defective, or, as Streeter would say, they are "bad eggs."

*Ovarian Agenesis and the Differentiation of Sex.*—In these cases, the fetuses developed the female features normally, even though there was no ovarian

follicular epithelium. In other words, the fetus had no functioning gonad; in spite of that, sex seemed to be differentiated normally, the female organs developed and the male organs retrogressed as they should in a normal female fetus. Wilkins and Fleischmann have posed the interesting question as to what controlled this sex differentiation and development in these cases.

It seems that the above cases prove that sex differentiation of the female is not controlled by the gonad of the fetus. The differentiation and development of the sexual apparatus may be initiated and controlled entirely by the chromosome constitution of the fetus, established at the time of fertilization. The maternal hormones may also play a part. This makes one wonder, as Wilkins and Fleischmann suggest, what would happen in a similar situation to a male fetus without any testicular epithelium. This question cannot yet be answered because no such case has yet been reported, as far as I know. These are complicated problems that are best left to the embryologists.

*Malformations of the Müllerian Ducts.*—Associated with this group of malformations, I generally find other lesions of the urogenital fold, and occasionally defects in the cloaca, bony pelvis, and intestinal tract; all of these organs are closely related in their development. Practically any variety of anomaly of the urinary tract may occur; I have listed horseshoe kidney, crossed ectopy, solitary ectopic kidney, absence of kidney, exstrophy of the bladder, and double ureter and kidney. Vulvovaginal anus and double kidney and ureter were associated in one instance.

The association of genital with urinary anomalies has long been an established fact. Thus, in 1923, Eismayer<sup>3</sup> reported that the homologous kidney was missing in every case of ovarian agenesis that he found in the literature. In 1944, on the basis of autopsy studies, Nation<sup>4</sup> found that 44 per cent of women with absence of one kidney had developmental defects in the reproductive organs. Clinically, these observations have been repeated so many times that it seems superfluous to state again that in every case of congenital malformation of either the genital or urinary tract in either men or women, the whole genitourinary system is to be studied.

Finally, I am forced to wonder whether solitary ectopic kidney is as rare as the literature would lead one to suppose. Thus, in 1944, Lowsley and Menning<sup>5</sup> reported a case of solitary ectopic kidney, stating that theirs was the thirty-sixth case to be reported in the literature. I wonder whether this rarity is not more apparent than real, although I do not mean to infer that it is a common finding. I am herewith reporting a case personally observed, and am quite sure that my associates on the gynecologic and urologic staffs have seen half a dozen more in the last few years. Miller and co-workers<sup>6</sup> and Brady<sup>8</sup> each reported a case in 1945, in discussing methods of constructing the vagina.

It is not only scientific interest, however, which should compel one to make complete examinations of the whole genitourinary system in these cases. In 1944, Lowsley and Kirwin<sup>11</sup> quoted Thompson-Walker to the effect that in 18 recorded instances, solitary kidneys had been removed surgically, always followed by death from uremia. In several of the cases of ectopic kidney which we are reporting, these unusual masses were first discovered by surgical explora-



tion rather than by intravenous urography and adequate preoperative genitourinary investigation. In view of these data, the need of adequate preoperative urologic study can hardly be overstressed in patients with congenital malformations of the reproductive organs or with unusual pelvic or abdominal masses.

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### Discussion

DR. HOUSTON S. EVERETT, Baltimore, Md.—In pointing out the coincidental occurrence of gross developmental anomalies in the genital and urinary tracts, Dr. Wharton has brought further evidence to bear upon the advisability of gynecologists and obstetricians being urologically minded.

Anomalies of the bladder and urethra in the female are rare, but anomalies of the upper urinary tracts occur very frequently and are of many varieties. Dees at the Duke University Hospital found anomalies of the kidneys or ureters in 135, or 9.6 per cent, of 1,410 consecutive patients subjected to pyelographic study. Eighty-six, or 73.7 per cent, of these anomalies were found in female patients. Gutierrez has stated that, in his experience, 40 per cent of all pathologic conditions of the kidneys and ureters are due to congenital anomalies.

As pointed out by Dr. Wharton, such anomalies may occur in individuals presenting gross anomalous development of the genitals, but they are found much more frequently in women with anatomically normal reproductive organs. The former group presents no points of interest for the obstetricians, since the individuals in it are incapable of reproducing. In the latter group, however, are found individuals who present points of interest in the obstetric as well as the gynecologic fields. Some of these patients may be enumerated as follows:

1. The anomalous kidney is more prone to disease than the normally developed one. It is therefore more likely to give rise to serious difficulties such as pyelonephritis complicating pregnancy.

2. The ectopic pelvic kidney, whether of the single or fused variety, may be mistaken on pelvic examination for an adnexal mass or a uterine tumor.

3. Such pelvic kidneys may cause dystocia. Six such cases were presented before this Society by Cragin in 1898, and a number of others have been added since. At least two cases, one by McGown and one by Ocherblad and Carlson, have been reported in which injury to an ectopic kidney from compression during labor has resulted in death from renal failure.

Finally, a few years ago we had the opportunity of following during pregnancy a patient with a fused kidney lying entirely within the pelvic cavity. To avoid the possible complications just mentioned, the patient was delivered by cesarean section. The point of major interest was that excretory pyelograms made every few weeks throughout the pregnancy revealed that no evidence of hydroureteronephrosis developed. As the ureters and pelves lay

entirely below the pelvic brim, they were not subjected to compression between the brim and the enlarging uterus, thus demonstrating the importance of the mechanical factor of compression in the causation of the so-called physiologic dilatation of the pelvis and ureters of normally placed kidneys during pregnancy.

DR. LOUIS E. PHANEUF, Boston, Mass.—The work of Albright, Wilkins, and Fleischmann has brought out the fact that in some cases, so-called ovarian failure may be due to agenesis or lack of follicular epithelium, whereas prior to their work ovarian failure was usually ascribed to lack of normal gonadotropic stimulation of the ovaries. Rudimentary ovaries are found associated with the partial or complete lack of follicular epithelium. As might be expected, the underdevelopment of the external genitals, the vagina, the uterus, and the uterine tubes is a concomitant of agenesis of the follicular epithelium of the ovary. Dr. Wharton points out that partial agenesis of the follicular epithelium of the ovary, where ovarian follicles, although decreased, though not entirely lacking, may account for some cases of oligomenorrhea in certain individuals who menstruate once or twice a year. If this way of thinking is acceptable, it explains the uselessness of administering gonadotropic therapy in such cases. It is brought out by the essayist that the various congenital malformations in certain persons affected by agenesis of the follicular epithelium, indicate that the genetic disturbance is general and not limited to the urogenital fold, as in the case of Müllerian duct malformations.

Dr. Wharton reports from his own experience the cases of six women with congenital anomalies of the Müllerian ducts and associated malformations. (1) Bicornate uterus in association with exstrophy of the bladder and separation of the symphysis pubis; (2) absence of the uterus with crossed unfused ectopy of the left kidney; (3) absence of the vagina and the uterus associated with absence of the right kidney and ectopic right ovary; (4) absence of the vagina and the uterus, absence of the right kidney, ectopic solitary left kidney in the sacral hollow, bilateral undescended ovaries, dermoid cyst of the right ovary, papillary cystadenoma of the left ovary, and situs transversus of the large intestine; (5) absence of the vagina and the uterus with absence of the left kidney and solitary ectopic right kidney; and (6) vulvovaginal anus with malformation of the right kidney and ureter.

It is obvious from the foregoing that complete urologic studies are essential in the examination of women with congenital defects of the reproductive organs. The modern methods of investigation have greatly simplified this problem. The most common lesion of the Müllerian system for which treatment may be applied is congenital absence of the vagina. The formation of an artificial vagina by Dr. Wharton's method is readily accomplished and is devoid of any great risk. From Sept. 9, 1943, to Jan. 31, 1944, I have operated on three young women by this procedure.

A few years ago, in my office, I saw a young woman who had complete absence of the vagina and uterus. She was referred to my clinic at the New England Medical Center for laboratory and x-ray studies. Within a few months, she brought three other young women with the same affliction. They ranged in age from 17 to 20 years. The mothers of these four girls were sisters, and two patients in each group were also sisters. They were advised to have artificial vaginas constructed when they contemplated marriage.

Dr. Wharton concludes his paper by stating—"In view of these data, the need of adequate preoperative urologic study can hardly be overstressed in patients with congenital malformations of the reproductive organs or with unusual pelvic or abdominal masses." This statement cannot be too strongly emphasized.

DR. ARTHUR H. CURTIS, Chicago, Ill.—I wish to call attention to a clinical observation which has been very helpful to me at the time of operation. If one notes congenital anomalies on the external surface of the body, it is my experience that we shall encounter congenital deviations from the normal within the abdominal cavity, such as Jackson's membranes, mechanical appendicitis, double uterus, and congenital convolutions of the tubes. Often, we are thus forewarned that we should look for a Meckel's diverticulum or urinary tract anomalies.

Among external abnormalities which may arouse suspicion of internal defects are unusual length of distance from the symphysis to the navel, supernumerary nipples, or moles and axillary breast tissue. From the perineal aspect, many deviations are suggestive, such as increased distance of the anus from the examining table, anomalies in the distance between the anus and the vagina, deviations in conformation of the perineum, and distortions and malformations of the external genitals, including increased distance between the meatus and the clitoris.

DR. WHARTON (Closing).—Dr. Everett's discussion brings out the point that many of these women have no obstetric complications. The last one I saw, however, came to me because of habitual abortion. We do not know the cause of that, whether there might be some type of urinary malformation or not. She has some small myomas in addition. The fact that a person has an ectopic kidney may lead to trouble in constructing the vagina. The ureter runs across the pelvic floor, and, if there is no point of cleavage, you might cause an accidental injury in that ureter. So that, in a solitary ectopic kidney you have to watch out for the ureter.

## LIFE AND WORKS OF ROBERT MEYER\*†

EMIL NOVAK, M.D., BALTIMORE, MD.

ROBERT MEYER was himself not, except in the earlier years of his career, a clinician, and yet there are few, if any, whose scientific contributions have been of greater importance to the clinical gynecology and obstetrics of our times than have been those which he has made. In the field of gynecologic pathology, he has been *facile princeps* for the past generation or more, with also to his credit many important contributions in the field of reproductive endocrinology. Throughout his professional career he has maintained a continuing interest in embryologic research, and some of his contributions in this field have been of monumental importance. Indeed, it is likely that his greatness as a pathologist is due in no small measure to his profound knowledge of embryology, and he himself has constantly emphasized the indispensability of the latter in the elucidation of many pathologic problems.

While a product of the German school in the heyday of its glory, Meyer's sunset years have been spent in our own country, thanks to the exclusiveness of the Hitlerian regime, now so ingloriously ended. He is now a proud American citizen, he has had many American students, he has through his writings instructed and inspired all of our growing American school of gynecologic pathologists, and he is an Honorary Fellow of this Society, as well as of numerous other organizations in this country. In his later years he has belonged to us, and it seems fitting that in our archives there should be preserved some record of the life and accomplishments of this outstanding personality in the history of our specialty.

So far as I know, none but the briefest and most inadequate biographical accounts are available in the country of his birth, and he himself has been too modest to write the autobiography which many far lesser men in our own profession have felt that the world expected of them. Many of us who, like myself, enjoy his friendship, and who are familiar with his scientific attainments, are painfully lacking in knowledge of his background, his early life and education, the forces which influenced him at various phases of his career, his avocations—in short, of all those human details which, to many, are a more illuminating record of a man's career than a cold recital of his purely professional accomplishments.

For most of such details which I have included in this sketch, I have had to assault Dr. Meyer's well-known modesty and reticence and dig them from the reluctant storehouse of his own memory of the happenings in his life. His reward must come not only from my own appreciation, but from that of many friends and admirers who will undoubtedly be glad to learn something of the

\*An address delivered at the Sixty-Ninth Annual Meeting of American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

†For lack of space, only a portion of this address can be included in our pages. The complete article may be found in the Society's Volume of Transactions for 1946, and in the author's reprints.

purely personal characteristics of one who is perhaps known to them, as he will surely be known to posterity, as one of the great figures in the history of our specialty. For additional information and reminiscences of Dr. Meyer, I am indebted to some of his former American students, as well as a number of German friends who preceded or followed him in expatriation from their native land.

In spite of the fact that, as he tells me, Dr. Meyer has never kept a diary and never made a point of preserving letters, his still remarkable memory yields many interesting and illuminating details of his early life. He was born in Hannover on Jan. 11, 1864, so that at this writing he is more than 82 years old. He remembers his grandfather, who was more than 74 years old when Robert was born. He had already retired from his business, which was that of banking, and had become seriously interested in the age-old effort to manufacture diamonds artificially. Meyer describes his grandmother as a woman of extraordinary charm, who, in spite of her age and the crippling ravages of arthritis deformans, completely dominated her family of eight children. In addition, and this Robert remembered well, she still knew how to bake wonderful cookies for no less than thirty grandchildren.

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After passing what he calls the most difficult examination of his life, Meyer was ready to follow his older brother to the University at Leipzig. Soon after that his brother became ill, and died shortly of a brain tumor.

It was at Leipzig that Meyer came under the influence of Wilhelm His, with whom he began his studies in anatomy, histology, and embryology. At the Carnegie Institute of Embryology in Baltimore, one can today find a collection of His's own slides, donated by Robert Meyer a number of years ago. In Leipzig, too, he learned to know Thiersch, famous not only because of his transplantation of skin, but also because of his caustic wit. A story about Thiersch concerns King Albert of Saxony, who expressed a wish to witness an amputation. After dextrously amputating the limb, Thiersch saluted the monarch with his saw and then sarcastically said, "Does your Majesty wish the other leg also?"

During the summer of 1884, Meyer studied at Heidelberg, taking comparative anatomy under Gegenbauer and physics under Bunsen. He says that these two great teachers kept him so busy he had time for little else, but this may be questioned, since at about this time he became engaged to his cousin, three years younger than himself, and the daughter of his mother's brother. However, they were not married until six years later. At the close of the summer he proceeded to Strassburg, which had become a German town at the close of the Franco-German war in 1871. There he came under the tutelage of a remarkable group of men. Among them were Gustav Schwalbe, a student of the great Ernst Haeckel; the physicist Kundt who, as Meyer says, experimented so infallibly, and the pathologist von Recklinghausen, who had been the very first assistant of the great Virchow himself. From von Recklinghausen, who in 1863 had discovered the migration of the blood cells in inflammation, and who had also in the same year detected bacteria in tissues,

he learned the fundamentals of pathology, the art of dissection, and the technique of cutting sections by hand, as well as staining them by the natural dyestuffs then available, cochénille and carmine. Although interested in the subject, at this time Meyer did not have any plans or ambition to become a pathologist himself.

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The most brilliant of the Strassburg teachers was the internist, Adolf Kussmaul, who had been a country doctor, but who became such a wonderful diagnostician that when he retired in 1887, von Recklinghausen could say of him that not once at postmortem was he able to reverse Kussmaul's diagnosis. Kussmaul used to complain that "now that we have the thermometer, doctors have forgotten how to diagnose by feeling the pulse." How familiar this sounds today, when a similar plaint is so often heard that the high development of laboratory methods has led doctors to forget the value of the five senses in diagnosis.

The gynecologist and obstetrician at Strassburg was Wilhelm Alexander Freund, famous because he had performed the first hysterectomy for cancer of the corpus uteri in 1878 on a patient whom he could exhibit eighteen years later before the German Gynecological Society at its meeting in Breslau. And yet his pride in this success was less than his resentment that there had been no great acclaim of his work on parametrial inflammatory disease, a type of mental reaction not uncommon among authors and investigators. He is described as a born teacher, whose large lucid eyes, as Meyer remembers, literally illuminated the audience and held it spellbound. Of the remaining Strassburg teachers, Meyer recalls also Heinrich Bayer, who taught theoretical obstetrics, and who wrote on pelvic anatomy and the development of the female sex organs.

On his first day in Strassburg, which happened to be the anniversary of the University, Meyer had been fortunate in meeting a freshman, Curt Neugebauer, who helped him greatly in making his plans, and with whom he formed a close friendship, continuing to the present day. It was in Strassburg also that he fulfilled his military service (1886), and he found this a not at all disagreeable interruption of his studies, although marred by an accident in the form of a fracture of the malleolus. However, as he slyly remarks, this yielded him a pension of nine marks monthly for twenty years. As another instance of high finance, on two occasions (1887 and 1888) he led a party of four students on tours of Italy, since he alone spoke Italian, the total expenses of these regal tours amounting to one hundred marks (\$24) per person. He had achieved considerable distinction as a singer, and in Strassburg he became the leader of the tenor section in the choir of the Academy of Music.

Among his fellow students were not a few whose names have helped to make medical history. For example, there was Ludwig Aschoff, who later became the famous pathologist of Freiburg, a man of joyful temperament and an eloquent teacher who attracted students from many countries, especially Japan. He and Aschoff became fast friends at Strassburg, and this friendship continued throughout their later lives. Meyer still prizes a small bronze relief of Aschoff presented to the latter by his friends on his seventieth birthday. Another student was August Wassermann, known for his work in syphilis,

and still another Wilhelm His the younger, the discoverer of the His bundle in the heart. Yet another was the gifted Robert Müllerheim, who later demonstrated the first roentgenograms of the living child in utero. He became the assistant of the gynecologist Freund, but Meyer admired him especially because of his love of art, the ancient classicists, and etymology. Meyer saw much of him in later years, when Müllerheim had taken up gynecologic practice in Berlin.

And then came the day of final examinations, and it was with Müllerheim and Neugebauer that Meyer appeared before the examiners. All were passed with flying colors, and were congratulated by Hoppe-Seyler, the dean, the date being Dec. 29, 1888. Shortly afterward they submitted their theses for the doctorate, Meyer's title being "Ein Fall von statischen Reflexkrampf." In the selection of this thesis he was influenced by Professor Tolly, the neurologist.

Meyer had already made plans for his immediate future, and in these he appears to have been largely influenced by Kussmaul, who would often invite students to his home in Strassburg, and who urged that country practice afforded the best opportunity for the young doctor to learn medicine. Meyer had been much impressed, and had already decided to follow this advice. Instead, therefore, of seeking an assistantcy, he went to Berlin to study as a "voluntary" at the Krankenhaus am Friedrichshain, becoming interested chiefly in the urological clinic of Fürbringer, who had written an excellent textbook on his specialty. He remained here some months, utilizing the remainder of the year 1889 to learn other things in various fields in preparation for his contemplated work as a country practitioner. It was during this period that he learned to know Robert Koch, the father of formal bacteriology. He describes him as a very serious man, who spoke very little. I can personally endorse this impression, because many years later, when I was a medical student, I had the honor of meeting the great Koch in Baltimore, which he visited during his lecture tour in this country. He impressed me as cold, unmagnetic, and taciturn, and I particularly recall that the hand which I so worshipfully shook had about the same feel as a cold fish.

And now our future great scientist was ready to begin his short career, destined to last four and three-fourths years, as a country doctor. Through a newspaper advertisement which his mother had clipped and sent him, he was led to the village of Dedeleben, a town of 2,100 people, taking over the practice, the house, three horses, buggies, and sleigh of a retiring country doctor.

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Life moved on very agreeably, in spite of the rigors of practice. There were frequent excursions to the Harz mountains, with often calls to distant patients on the way. Meyer was a regular attendant at the regular monthly medical meetings in near-by Halberstadt, a town of 25,000 people. A prominent figure at the meetings was Hans Kehr, later a famous surgeon in Berlin, and even then rapidly achieving distinction in the field of gall bladder surgery. His two large volumes on this subject are well known to surgeons.

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And then, in 1895, came an event which proved to be a turning point for Meyer, since it appears to have deflected the current of his life into the channels of gynecologic pathology. One day, at the home of his uncle, he met a doctor who asked him whether or not he was too busy to serve as "volunteer" in the private clinic of Johann Veit, also professor of gynecology at the University. Veit had written an excellent monograph on tubal pregnancy, and was the editor of the *Handbuch für Gynäkologie* (1897). After his death this office was taken over by Stoeckel, and the Veit-Stoeckel *Handbuch* has remained perhaps the most popular reference work in its field.

Meyer describes Veit as a very genial man, though his geniality was perhaps a bit overaccentuated. In his private clinic he operated with his two regular assistants and Meyer, who, in addition, was put in charge of the pathologic laboratory, a tiny room about the size of a large closet. In these simple quarters began Meyer's career as a pathologist. He still kept up his practice, and for fear of missing professional calls, fitted up a room in his own home as a supplementary laboratory. He had a microscope, and, since he had to be his own technician, he purchased a microtome, soon becoming expert in the preparation of sections and in microscopic diagnosis. He still has some of these early sections, including some through the whole kidney, indicating what a virtuoso he had become.

In about 1896, Johann Veit accepted the chair of obstetrics and gynecology at the University of Leyden, in Holland. Before leaving Berlin he suggested to Meyer that if he were at any time in need of material or of counsel, he consult Carl Ruge, the prosector of the University Gynecological Clinic. At this time Meyer took a course in practical embryology with Oscar Hertwig, who had given the first description of the process of fertilization (in the sea-urehin), and who had written what Meyer calls a wonderfully clear book on general biology, from which he had learned a great deal. He also met Paul Ehrlich, the discoverer of salvarsan.

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Carl Ruge, who now began to play an important part in Meyer's life, had worked under Virchow, and in 1869 had won the University prize for his excellent work on the pathology of the bones. He was born in 1846, the son of a physician, and a nephew of Virchow's wife, who in turn was the daughter of the famous gynecologist, Carl Mayer. After the Franco-German war (1870 to 1871) Ruge became assistant in the University Frauenklinik, and when the clinic acquired its own pathologic institute in 1887, he was advanced to the post of prosector. Like Meyer, he continued as a busy practitioner, but retained his direction of the pathologic institute until 1912, when he was succeeded by Meyer. It is Ruge and Veit, but especially the former, who deserve the credit for the beginnings of gynecologic pathology, while Meyer, the successor of Ruge, later became the recognized world leader in this special field.

It is to Ruge and Veit also that we are indebted for the introduction of biopsy as the only possible means of early and certain recognition of cancer of the cervix (1878) and of curettage as a corresponding diagnostic procedure for

carcinoma of the corpus (1881). Ruge fought valiantly for his views, against which there was much opposition, and he constantly urged that gynecologists make themselves independent of pathologists by becoming pathologists themselves. This idea, after a great many years, appears to be coming to its own, as judged, for example, by the insistence on some knowledge of pathology as one of the requirements for certification by our American Board of Obstetrics and Gynecology. With Ruge, Meyer began a warm friendship which continued for thirty years, and which was strengthened by the marriage of Ruge's daughter with Mrs. Meyer's brother. At this wedding Meyer states that no less than 108 relatives of the Ruges were present.

It was in 1903 that Meyer first made contact with Lubarsch, then the pathologist at the Academy of Medicine in Posen. This first contact was not altogether a pleasant one. Lubarsch was, of course, a highly trained biologist and pathologist, and among other things he had founded the *Ergebnisse der Pathologie*, which he edited until his death in 1933. However, he was an arbitrary, dictatorial, and pugnacious individual, who seemed to stir up trouble wherever he was. One of his pupils, Arthur Stein of New York, had published a paper describing a case in which the diagnosis was carcinoma of the Müllerian epithelium, and Meyer, in a letter to Stein, had taken issue with this diagnosis. Since it was Lubarsch who had really made this diagnosis, Meyer promptly received from the latter an offensive reply, and half an hour later he visited Lubarsch, who happened to be visiting his mother in Berlin. His reception was cool and haughty, but Meyer knew his embryology as few others did, and soon convinced Lubarsch of his error. Eight days later, a letter came from Lubarsch inviting Meyer to write on embryonal failures in female sex organs for the *Ergebnisse*, and one year later a masterly review of the whole subject, comprising 200 printed pages, was in Lubarsch's hand. The pathologists of the country began to ask "Who is Robert Meyer?" At this time he was still a private practitioner, with the same brass plate, reading "Physician and Obstetrician," on the front of his house door.

In March, 1908, Meyer received what he describes as a startling offer, and one which changed the whole current of his life. The great Ernst Bumm, was then the head of the Charité Clinic, and through his assistant, Lippman, Meyer was offered the directorship of Bumm's laboratory, with the title of professor. He was then 44 years old, and he asked for three days to make his decision. At the end of that time the brass plate came down from the front door, and henceforth the busy practitioner with the love for pathology entered academic life as a pathologist.

Bumm, whom Meyer knew as president of the Gynecological Society, was an agreeable chief, and easy to work for. When he was later transferred to the University Clinic on Artillerie-strasse, a Mecca for American gynecologists of a generation ago, Meyer remained on at the Charité for two additional years with Rudolf Franz, Bumm's successor at that clinic. Many of us will remember Franz as perhaps the most skillful operator in Berlin, and a splendid teacher as well. He and Meyer remained fast friends until Franz's death at the prime of his life, as a result, incidentally, of dysgermonoma or seminoma of the testis.

During his Charité days, Meyer, with the enormous amount of material now at his disposal, was increasingly productive. His published works during this comparatively short era included studies on the Wolffian duct, the development of the male genitals, the utriculus prostaticus, the mesonephros and the nephric intermediate blastema, metanephric vestiges in the inguinal region, and congenital abnormalities of the kidney. Throughout all these studies, his deep interest in and his profound knowledge of embryology are clearly manifest. In 1911, he published his comprehensive monograph on embryonal anomalies in general, including those of the male sexual organs, for Lubarsch's *Ergebnisse*, with another comprehensive article on the same general topic the following year in the *Zeitschrift* (1912). In both these works he discussed many fundamental problems in masterly fashion. Among other things he emphasized that Cohnheim's well-known theory of embryonal inclusions as a cause of tumor formation was inadequate, since most such tissue inclusions ripen to normal tissue. He insisted that it is the indifference or immaturity of the embryonal tissue which is essential to tumor formation.

In 1912, Meyer moved over to the Artillerie-strasse clinic with his old chief, Ernst Bumm, becoming the successor of Carl Ruge as prosector of the Pathological Institute. Many of the older Fellows of this Society will have pleasant memories of the courtly and aristocratic Bumm, and of his gifts as a clinician and teacher. Bumm was an artist, and, indeed, had planned to become a painter before he embarked on the study of medicine. Many of us will recall how, with a piece of chalk in each hand, he would stand before the blackboard, and within a few moments produce an astonishingly graphic visualization of the particular point he wished to impress on his audience. His textbook on obstetrics was the best of its day, and, incidentally, he was the royal accoucheur in the prolific household of Kaiser Wilhelm.

And now Meyer began his important series of publications in the field of ovarian tumors, in which he had always been interested. It is probable that his contributions in the study of ovarian tumors are better known, at least in this country, than any of his numerous other activities. In 1914, he wrote on adenoma tubulare malignum, and in 1915 came the paper on carcinoma ovarii folliculoides et cylindromatosum, in which he discussed for the first time the histogenesis of a group of tumors from granulosa cells dating from a very early phase of ovarian development. There soon followed studies of the normal and pathologic anatomy of the medullary cysts and tubules and of the rete ovarii, though these studies were not published until 1920 because of the interruption of World War I.

During the war, Meyer served on the staff of a military hospital in the outskirts of Brussels, his work including not only general and orthopedic surgery, and the treatment of venereal diseases, but also the conduct of the x-ray laboratory. Occasionally he was called upon to escort numbers of insane or venereal patients back to Berlin, these trips giving him an opportunity of visiting his family. However, he had more frequent opportunities of seeing his son, who was stationed on the western front. During the "flu" epidemic of 1918, the son was desperately ill with bilateral pneumonia, and Meyer was

allowed to nurse and care for him during his illness, from which he fortunately recovered, though he later had no recollection of his father's presence.

His scientific work was certainly not forgotten during his absence from his laboratory, because he somehow found time during this period to publish his paper on the histogenesis and classification of ovarian tumors, and another on rare ovarian tumors. In the latter, he describes not only the granulosa-cell type, but also a tumor in a girl of 10 years, belonging to the group to which he later gave the name of dysgerminoma.



Meyer (the bearded officer on the stairs) behind two German princes, chiefs of the Red Cross, at a hospital in Brussels where Meyer was stationed in World War I.

He had little time for reorientation and refamiliarizing himself with the literature, for soon after his return Lubarsch, now the pathologist at the University in Berlin, called on him to write the section on "Pathology of the Uterus," and also on hydatidiform mole and chorionepithelioma, for the famous Hencke-Lubarsch work on *Specielle Pathologie*, and to delegate other sections dealing with the female generative organs to whomever he might select, with the exception of the chapter on "Pathology of the Ovaries," previously committed to J. W. Miller. At the same time, he accepted the responsibility for the preparation of a number of chapters for the Veit-Stoeckel *Handbuch* (Vol. VI). These publications did not appear until about ten years later. They cover the whole field exhaustively and authoritatively, so that even today they remain the chief sources of our knowledge of the many subjects covered by Meyer.

In 1923, he was invited to lecture and to give a course in microscopie pathology in Oslo (Norway), and also in Upsala (Sweden), and he was greatly impressed with these countries and their professions. During all of this time articles flowed from his laboratory and pen, as a glance at his bibliography will show. His sixtieth birthday was recognized by the Berlin Gynecological Society, and on this occasion his chief and friend, Bumm, expressed the Society's congratulations in his characteristically kindly and eloquent manner. At the end of this year Bumm died quite suddenly, and Meyer was called upon to speak at the mass for the dead. The entire clinic was grief-stricken, for Bumm was universally loved and respected, and Meyer felt his loss very keenly.

During the rather long interim before Stoeckel was appointed to succeed Bumm, Meyer gave weekly evening lectures to the clinic assistants, in order to keep up the spirit of the clinic. The new Geheimrath was a striking contrast to his predecessor, being of rather typical, formal Prussian temperament, and lacking the kindness and geniality of Bumm. However, he was a prodigious worker, and his deep interest in both the patients and the staff won him general respect. He was the editor of both the *Zentralblatt* and the *Zeitschrift*, and later found time to create a new *Zeitschrift*, that for Gynecological Urology, in which his greatest interest lay. Moreover, he was the editor of the third edition of the Veit *Handbuch*, to which he added three large volumes on Gynecological Urology. He is described as being a gifted orator and a splendid teacher. Stoeckel and Meyer, so different in many of their personal characteristics, soon developed much respect and admiration for each other's gifts, and they became fast friends. Contrary to what many have believed, Meyer insists that Stoeckel has never been a member of the Nazi party, though he contributed to it by delivering two little Goebels.

Stoeckel showed his esteem for Meyer in many ways. For example, when Prof. Heller, the pathologist at Kiel, died, Stoeckel proposed Meyer as his successor. However, Lubarsch was chosen, but Meyer was not disappointed, for he preferred his agreeable position in Berlin. His productiveness continued unabated.

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In 1924, Meyer took rather sharp issue with Corner and other American anatomists in their introduction of the term "anovulatory menstruation," holding that only the cyclical physiologic bleeding which is preceded by ovulation and progestational changes in the endometrium should be spoken of as menstruation. In this view he was supported by Schroeder, and he still maintains the viewpoint in his most recent publication, appearing in the January, 1946, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. On the other hand, the American investigators have likewise not receded from their position, and the term as well as the concept of "anovulatory menstruation" seems to have entrenched itself rather securely, at least in this country.

During these years Meyer contributed many abstracts and reviews to the well-known *Berichte ü die gesamte Gynäkologie u Geburtshilfe*, and in 1928 he prepared for this publication a very exhaustive review on the function of the

ovary, especially the corpus luteum. It is a complete storehouse of knowledge of all aspects of the subject up to that time, with a bibliography of about 250 references.

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The year 1930 is an important one in Meyer's life, because it marked the publication of a number of classic papers on special ovarian tumors, the contribution for which he is perhaps best known to American gynecologists. Three papers dealt with the subject of the masculinizing tumors of the ovary, to which he gave the name of arrhenoblastoma, applying this term not to any one stereotyped histologic form, but to a whole series of gradations made possible by the development of such tumors from certain originally male-directed elements in the ovary, the tumors reproducing testicular characteristics with varying degrees of imperfection. He divided this tumor group into a ripe, unripe, and intermediary variety, showing that the so-called testicular adenoma described many years earlier by Ludwig Pick really represents the highly differentiated variety of arrhenoblastoma. He also described in perfect detail the sequence of defeminization and masculinization phenomena produced by these tumors, and regressing after their removal.

In another paper during the same year he described as another definite group the granulosa-cell tumors, a number of which had been previously reported by von Werdt and others, although often confused with tumors of totally different nature and origin. With the granulosa-cell tumors, as with arrhenoblastoma, he gave us a perfect description of the feminizing effects produced at various age epochs. The third important tumor derived from cells dating back to an early undifferentiated phase of gonadal development he designated as a dysgerminoma, with no effect on sex characteristics. This tumor type, the "gross-kerniges or gross-zelliges karzinom" of previous German writers, had for many years been misinterpreted by all pathologists, but Meyer gave us a sharply drawn description of its histogenesis, gross and microscopic characteristics, as well as its clinical implications.

As the fourth member of what he then included as the "special tumors" of the ovary, he delineated the Brenner tumor, previously described but wrongly interpreted, under such designations as oöphoroma folliculare. He also demonstrated that in the cystic form there may be a pseudomucinous transformation of the epithelium, with at times the production of even large pseudomucinous cystadenomas. Most of us would be satisfied to have made even one such contribution, as is represented by Meyer's classical studies on this tumor group, and yet it was only one episode in his productive life as a pathologist.

It was this particular subject which he chose for his address before the American Gynecological Society as its foreign guest in 1931. It was not until the year before, he says, that he began to study English, although he had, of course, a reading familiarity with the medical literature in that language. When the cabled invitation to speak in America came from Dr. Graves, our president of that year, he was quite thrilled, and amusingly states that he and

Mrs. Meyer had a long debate, finally deciding for acceptance. She then reminded him that he ought to cable his acceptance, but he told her that he had already done so on the way home.

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But the steady stream of Meyer's scientific productiveness flowed steadily on. To show the diversity of his interest, he made an exhaustive study of the so-called "myoblasten myoma" of Abrikossoff, arising from a special type of myoblast in the muscles of the throat and mouth regions, as well as the muscle elements of the skin. Again, in papers by himself and by two of his old students, Kaufmann and Aschheim, he reverted to the subject of the proliferative phase of the corpus luteum, the existence of which was doubted by the French pathologist, Moulouguet, with whom an interesting controversy thus took place.

The year 1932 is marked by the beginning of Meyer's monumental study, which was to continue for many years, on the development of the human vagina. This, to my mind, represents perhaps his most important scientific contribution. It was during a period of political turbulence in Berlin that he sought solace in this study of "constitutional embryology," as he likes to call it. For this long and patient study 112 fetuses were cut serially, although in the larger fetuses only the pelvic organs were thus sectioned, while in 14 others special sectioning of various anomalies was done. From this large material he made about 3,000 photomicrographs, which he collected in five large albums which were dedicated to Professor Stoeckel. These were deposited in the library of the University Frauenklinik in Berlin.

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In January of 1934 Meyer's seventieth birthday was honored by an imposing celebration in Berlin. Meyer was presented with a bronze bust of himself, the work of Fritz Klimsch, one of the best sculptors in Germany. The presentation address by Stoeckel expressed the admiration and affection in which Meyer was held in the gynecologic and pathologic worlds. He was the recipient of many congratulatory letters from all parts of the world, including messages from the presidents of the German Gynecological and German Pathological Societies, and the President (Rector) of the University. The latter expressed gratitude for all that Meyer had done and was still doing for the benefit of all connected with the University, from his oldest colleagues down to the youngest students. Stoeckel, in the course of his eloquent address in the presentation of the bronze bust said, "You began as a student and friend of Carl Ruge, who drew the first plough through the virgin soil of pathologic gynecology, but you have completely plowed the soil and planted it, so that hitherto barren stretches have been brought into full bloom, and much new land has been brought under cultivation. You are the creator of gynecologic histology and in this field you have become an unerowned king, a 'praeceptor mundi.' "

During this time the Nazis were becoming more and more powerful, and also more and more antisemitic, but Meyer was not disturbed in his position



until the end of 1935. And then the man who, less than two years previously on the occasion of his seventieth birthday, had been acclaimed by all his colleagues, was dismissed from his post at the university. Through the intervention of Stoeckel he was allowed to continue unofficially until the end of 1938, without salary, but with permission to retain the fees he earned from his large consulting pathologic practice. Since the latter yielded him no less than 24,000 marks annually, and since his salary had been only 6,000 marks, the financial loss was not so great, especially as his private income jumped to 30,000 marks within the year after his dismissal. But at the end of 1938



Bronze bust presented to Meyer at a celebration on his seventieth birthday.

the Nazi minister of the interior and the minister of education decided, as Meyer laconically states, that the German nation was now antisemitic enough to get along without him. During this trying time Stoeckel was very kind to him. Meyer was now busy with plans for his departure to America, and corresponded with some of his old friends and former students in this country, among them John McKelvey, through whom he was later offered a post at the University of Minnesota. He received permission to leave the country without being put under the quota, and this proved to be an immense advantage, since he got out of the country on almost the last train the very day the war broke

out. Through a friend in the customs, he was able to get out at least a part of his furniture and all of his scientific material.

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He continued his work at the University of Minnesota, with the rank of Associate Professor, until 1944, since which time he has been leading a quiet, but anything but idle, life. He is as intensely interested in work as ever, and at present is engaged in the study of the development of the ureter. He has also been a faithful and invaluable member of our Committee on Ovarian Tumors.

It must interest us all, in viewing the enormous scientific output of this man, to know something as to his methods of work, and I put just this inquiry to him. He tells me that he has always read every possible publication in his immediate fields of embryology, anatomy, biology, and pathology, as well as in many others, and that he made and filed abstracts of them, whether or not they bore on any problem in which he was at the time interested. He destroyed many thousands of these abstracts when he left Berlin, and still has many thousands which he will never use. He wrote all his papers in long-hand, often rewriting them three or four times. He says he could not write a paper from beginning to end, but would put down ideas as they occurred to him, these in turn suggesting new ideas as he wrote. Not a single one of his many papers, he says, has been written in good order from start to finish, all being rewritten perhaps several times. How a man who never seems to be in a hurry could accomplish all this is hard to believe.

Perhaps his own experience is responsible for his editorial policies during his long career as coeditor of the *Archiv für Gynäkologie*, and departmental editor of the Heneke-Lubarsch *Handbuch der Speciellen Pathologie*. He does not believe in any such thing as editorial standardization, preferring to allow the author all possible individuality of style and presentation, so long as the content of his paper is good.

By some he has been said to be unnecessarily critical in his writings. To be frank, I was inclined to believe this from his writings before I learned to know him. No one could be more modest and unaggressive, and what might seem to some to be arbitrariness is really only the authoritativeness which comes from assured knowledge. He is indeed much more critical of himself than of others, and likes to quote the words of a French scientist, "What I know, I do not know with absolute certainty; but what I do not know, I am entirely ignorant of."

A more complete biography of Robert Meyer would have to include a far fuller review and evaluation of his contributions than has been possible in this comparatively brief account. Furthermore, I have deliberately chosen to devote much of this paper to the human rather than the scientific aspects of his career, because such illuminating side lights, easily forgotten in a few years, should be preserved in our archives, while the scientific publications will remain an important segment of the literature of our specialty for many years to come. I have, however, taken pains to track down his publications as completely as possible, although I am sure there are some omissions in the

bibliography appended to this paper, imposing though it is with its approximately 200 references. This includes only his major publications, and not the innumerable discussions and demonstrations which he gave before many scientific gatherings. Nor does it take cognizance of the scores of important papers by his assistants and students, guided and inspired by Meyer himself.

My personal evaluation would be that his greatest contributions have been in the field of embryology, especially the embryology of the vagina. Perhaps next would be his work with ovarian tumors, especially the "special" group which he, so to speak, put on our gynecologic map. Others, perhaps, would consider of equal or greater importance his numerous contributions to the problem of cancer diagnosis, dating back to his early days with Carl Ruge, who first stressed the value of biopsy and curettage as decisive procedures.



A characteristic picture of Meyer at his microscope.

The endocrinologists, too, would not wish to have us underestimate the fundamental value of his studies of the corpus luteum life cycle or that of the endometrium, and the correlation of the two. And what about his publications on cervical erosions and epidermidization, hydatidiform mole and chorionepithelioma, endometriosis and adenomyosis, the hitherto almost untouched field of nerve tumors of the pelvis, and the elucidation of many types of genital and fetal abnormality? Many of these subjects are described in his contributions to the Handbooks of Veit-Stoeckel and Henke-Lubarsch.

The personal traits which have made his scientific career so rich and full, it seems to me, are his absolute intellectual honesty, his enormous capacity for work, and his rich endowment with that "equanimitas" which our own beloved Osler esteemed so highly.

He has a wonderful sense of humor, and I wish there were time and space to give some examples of the really sparkling wit with which his letters abound. He has this to say in retrospect about his own life. "I have had an exceedingly beautiful life which would be worth while living once more. I have had no sorrows except those which I made myself, and they were unimportant. I have always had the feeling in difficult situations that things would come out well, and they did. I let life approach me, made my decisions, and they were right. I did not seek or apply for any position. I had nobody to ask for recommendation. I was in every way independent. I worked for my own satisfaction. My life, without planning it so, was rectilinear. I have never been an assistant except for one short period, and have never had the ambition to be "privat docent" of pathology or anatomy, as might have been expected of me. I was an autodidact. I had no special plan and no connections when I began to study pathology at an age at which most men are already settled in a career. In retrospect, that course seemed to me quite reasonable at the time I did it, but why I did it, I do not know. It seemed to me important at the time. It happened that it offered me something, and whether or not I was to take full advantage of it, it was the right thing to do."

He has not been embittered by the fact that he was caught up in the savage and costly orgy of Hitlerism which has ruined his Fatherland, both economically and scientifically. He suffered grievous blows in the premature death of his cherished son, and in the loss only two years ago (1944) of his beloved and devoted helpmate of many years, but at no time has he inflicted his sorrow upon his friends. He is spending his sunset years serenely but not idly in a land far from the mother country which cast him off, but which could not rob him of the high position he had already achieved in the world of science. No greater name is inscribed in our roll of Honorary Fellows than that of Robert Meyer.

*(A complete bibliography of Professor Meyer's contributions to the medical literature may be found in the Society's Volume of Transactions, and the author's reprints.)*

# Original Communications

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## THE OFFICE STUDY OF INFERTILITY\*

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**A** PRACTICAL working procedure for the office study of sterility in the female directs the search for contributing factors into four main directions: (1) mechanical factors, (2) chemical factors, (3) endocrine factors, (4) general factors.

Mechanical factors are those which exist to impede or obstruct the union of the sperm and the ovum. They include the more or less common conditions of cervical strictures and secretions, retroflexed uterus, tubal occlusion. They are discovered in the course of the ordinary gynecologic examination, and with the aid of the insufflation apparatus devised by Rubin. Carbon dioxide in controlled amount and under controlled pressure is passed into the uterine cavity and, in the case of patency, through the Fallopian tubes into the abdominal cavity. Patency is demonstrated by kinographic tracings which, in addition, record the presence or absence of tubal peristalsis, by hearing the gas as it passes from the narrow lumen of the tube into the wider abdominal cavity, by visualizing in the fluoroscope the gas as it has accumulated under the diaphragm; and by the occurrence of shoulder pain. In the case of the badly infected cervix, mechanical factors may be introduced by thick, tenacious, or mucopurulent discharges. This may be seen by the method of Huhner of direct observation of the sperm as obtained from the cervical canal.

Chemical factors in sterility are studied by the method of Huhner and Kurzrock. A chemical imbalance may exist between the normally alkaline cervical secretions, normally acid vagina, and normally alkaline seminal fluid. In addition, infection may introduce chemical disturbances that are definitely destructive to the sperm. Direct observation of this is possible by obtaining postcoital samples for microscopic examination. The pH of cervical and vaginal mucosa may be determined by the use of suitable indicators.

The office investigator will find his endocrine studies limited to two practical and valuable observations. First, the determination of the basal metabolic rate. Litzenberg, in 1937, and many investigators subsequently have pointed out the importance of the thyroid-ovarian association. Definite hypothyroidism, and the less definite subclinical hypothyroidism, are important factors in sterility. Second, the determination of ovulation. The introduction of the aspiration curette by Novak has made this an office procedure. Endometrial biopsies obtained just before or in the first few hours of menstruation will show the typical

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\*Read at the Meeting of the South Atlantic Association of Obstetricians and Gynecologists at Greensboro, N. C., Feb. 15, 1946.

secretory endometrium showing the luteinizing effect of the ovary, and thus, by inference, the occurrence of ovulation.

General factors in sterility are emphasized by Meaker. By them are meant such conditions as anemia, foci of infection in tonsils, teeth, etc., pyclitis, nephritis, tuberculosis, etc. These are determined in the course of routine physical and laboratory examinations.

This series of cases under consideration consists of 210 women studied by all means available to us and according to the plan outlined. They are unselected, with no effort to evaluate any particular type of treatment. An attempt has been made to answer the questions: "What have we to offer the woman who complains of infertility for any reason whatsoever? How many of them will eventually succeed in attaining normal, viable offspring?" The series consists of cases in whom conception is obviously impossible, such as the congenitally abnormal and the surgically crippled. It includes cases incompletely studied and treated, due to change of residence, wartime dislocation, etc. In other words, it is the over-all picture of the kind of patient seen, the kind of treatment undertaken, and the kind of results obtained in our offices.

TABLE I. AGE OF PATIENTS

AGE (YEARS)	NO. OF CASES
20-25	25
26-30	67
31-35	55
36-40	23

It would appear that the woman's greatest desire for offspring occurs within the age group 25 to 30 years, and, similarly, her alarm at her inability to conceive brings her to the physician most often at that time. Under the stimulus of an even greater urgency, an almost equal number will appear between the ages 30 to 35 years. Five successful pregnancies occurred after the age of 36 years. The age of the husband was in line with the wife. In the group of cases in which pregnancy was successful, the oldest recorded age for the husband was 47 years; in those not successful, the oldest was 53 years.

TABLE II. YEARS MARRIED BEFORE SEEKING MEDICAL ADVICE

YEARS	CASES	PER CENT
1-5	102	53
6-10	69	30
11-15	22	11

Fifty-three per cent of infertile women will seek medical advice within one to five years of married life. On the other hand, 63 per cent of the women who subsequently become pregnant had consulted physicians by the time they were married five years or sooner. This would seem to confirm the impression that the longstanding, untreated case of sterility has the least satisfactory response when treatment is undertaken.

TABLE III. YEARS WITHOUT CONTRACEPTION

NO. OF YEARS	NO. OF CASES	PER CENT
1-2	64	33
2-3	27	14
3-4	39	20
4-10	62	32

The same thing is shown in principle when the number of years without contraception is considered. Although one-third of all women had consulted a physieian not later than two years without contraception, 50 per cent of the cases that subsequently became pregnant had been not longer than two years without contraception. In this series, no case was considered unless without contraception of any type for at least one year.

TABLE IV. PREVIOUS PREGNANCIES

TYPE	NO. CASES
No pregnancies	153
Abortions	
Induced	3
Tubal	3
Spontaneous	27
Term	
Stillborn	5
Living	11

Of the 210 women studied, 153 had had no previous pregnaneies; 49 were secondarily sterile inasmuch as previous pregnancies had existed. The record for these pregnancies was not good, however, since they represented only 11 living children, 30 had ended in abortions of which three had been induced, five were stillborn, and three were tubal pregnancies. Of the women who subsequently became pregnant under treatment, only two had had living children, one had had a full-term stillbirth, eleven had had abortions, and one had had an eetopie pregnancy.

Mechanical and Chemical Factors

Meehanical and ehemical factors in the sterility of this group were found or suspected on the basis of: (1) history; (2) ehemical tests such as the use of indicators in the vagina and eervix; (3) detailed examination of the reproductive traect such as the use of the sound, observation of the eervix and its seeretions; (4) palpation of the uterus and, sometimes, of the tubes; (5) the Huhner test which is an indiciator of both ehemical and meehanical abnormalities; (6) tubal insufflation as devised by Rubin; (7) lipiodol and x-ray studies of the tubes and uterus.

Although incomplete, the history alone was helpful, as may be seen in Table V.

With the exeption of gonorrhea, the part that these diseases played in the production of sterility due to injury to the reproductive meehanism is difficult to evaluate. It is interesting to note that of the patients who became pregnant, one gave a definite history of gonorrhea, 13 had had mumps.

TABLE V. HISTORY OF PREVIOUS SIGNIFICANT DISEASES

DISEASE	NO. OF CASES
Mumps	45
Gonorrhea, definite	5
Scarlet fever	7
Phlebitis	2
Pneumonia	11
Rheumatic fever	1
Tuberculosis	1
Streptococcic infections not classified	2
Typhoid	1
Typhus	1

TABLE VI. HISTORY OF PREVIOUS SIGNIFICANT SURGERY

OPERATION	NO. OF CASES	NO. OF WOMEN PREGNANT
Appendectomy		
Ruptured	4	0
Unruptured	54	
Suspension of the uterus	9	
Ovarian surgery (removal or resection)	19	4
Salpingectomy	5	1
Ectopic pregnancy	3	
Thyroidectomy	2	
Nephrectomy	1	
Dilatation and curettage	11	
Amputation cervix	2	
Cauterization of cervix	4	
Vaginal plastic	1	
Bartholin cyst	1	
Stem pessary	14	0
Smith-Hodge pessary	2	

A relatively high incidence of surgical manipulations of one kind or another was elicited from the history. This was particularly noteworthy in the patients with long-standing sterility.

None of the cases with a history of ruptured appendix became pregnant under our treatment. Two cases with a history of resection of the ovary became pregnant. Two cases with unilateral oophorectomy for endometriosis became pregnant. One case with a history of salpingo-oophorectomy for a ruptured ectopic pregnancy became pregnant. Two cases with bilateral salpingectomy were included in this series principally because they had presented themselves for study and received tubal insufflation more as an assurance as to their sterility than as a hopeful gesture. None of the fourteen cases with a history of having worn a stem pessary became pregnant or had a history of a pregnancy. In one case, the pessary was so imbedded and overgrown within the cervical canal that surgery was necessary for its removal.

It is logical to suppose that the normally alkaline semen would find in the normally alkaline cervix an environment favorable to spermatoc mobility and viability. Conversely, hostile chemical factors should exist where an abnormal cervical pH is present. Vaginal secretions were tested in 103 cases and were found acid in all cases. The pH of the cervical canal was tested in 101 cases; in 52 cases it was on the alkaline side and in 49 cases it was on the acid side.



What changes in cervical and vaginal chemistry occur in association with sexual stimulation and organism in the female cannot be measured. Theoretically, however, cervical secretions should have been unfavorable in the 49 cases. In respect to this factor, no appreciable difference was apparent in the cases becoming pregnant as compared with those not achieving pregnancy. Infections of the cervix and erosions of the cervix are in somewhat the same category. Both chemical and mechanical factors are unquestionably introduced by these abnormalities; the mechanical factors being seen in connection with the Huhner test where the enmeshed and entrapped sperm are so often seen struggling in the tenacious, mucopurulent exudate from an infected cervix. In 66 cases, an erosion of the cervix of sufficient extent to warrant recording was present. In 46 additional cases a deep-seated cervicitis was present, of which three cases had impassable strictures; in 11 more cases, laceration and infection were present. In all, 123 of these cases (59 per cent) presented outstanding cervical pathology, a most impressive figure. Vaginal pathology, such as *Trichomonas vaginalis*, fungus type of vaginitis, etc., were noted in nine cases.

TABLE VII. MECHANICAL-CHEMICAL FACTORS

TYPE	NO. OF CASES
pH vagina acid	103
pH cervix acid	49
pH cervix alkaline	52
Erosion of cervix	66
Infection of cervix	46
Laceration of cervix	11
Infection of vagina	9

TABLE VIII. UTERINE POSITION AS A MECHANICAL FACTOR

Retroflexed uterus in series	20%
Retroflexed uterus in pregnant cases	11%

The retroflexed uterus presents a mechanical factor principally in regard to the position of the cervix which is frequently observed to be out of the seminal pool. Forty-two cases (20 per cent of the series) were observed to have this abnormality. Since this is approximately the incidence among all women, the figure is not impressive. However, a somewhat different evaluation is obtained when it is noted that in the cases in whom pregnancy eventually occurred, only 11 per cent had a retroflexion of the uterus. In other words, it was only half as frequent in these women as in the general female population and in the rest of this series. Faulty position of ovaries and tubes occasionally described as "prolapsed into the cul-de-sac" and very frequently associated with abnormal position of the uterus, cannot be evaluated. But the palpable tube is an abnormal one. The tubes were described as palpable in five cases of which one had a frank tuboovarian abscess. Occult obstruction of the tube is demonstrable only by tubal insufflation.

We are in complete agreement with Meaker and Siegler, who point out that the study of sterility is not properly the investigation of individuals, but rather the study of infertile matings. However, in practice, the gynecologist will have

little or no direct contact with the male half of the problem, depending upon the urologist to balance the study. This may or may not be a fortunate combination but, in any event, since 30 to 40 per cent of sterility factors have been variously estimated to reside in the male, it is an important one. Our own series frankly considers the male indirectly: from his history as obtained from the wife, from the Huhner sperm test, and from condom-bottle sperm tests. The man is referred to the urologist for further studies on the basis of these contacts only. Here the Huhner sperm test was recorded 104 times, and was considered normal in 48 cases, abnormal in 56 cases. The condom-bottle sperm test was recorded 123 times and was considered normal as to count, motility, and morphology in 62 cases; abnormal in 61 cases. By this indirect approach, abnormalities in the male so far as observation of the sperm is concerned, would seem to exist in 50 per cent of the cases. A better appreciation of the role of the male in infertile matings is seen indirectly in the fact that 65 per cent of the husbands of the women who became pregnant had normal sperm, whereas only 44 per cent of the husbands of women failing to become pregnant had normal sperm.

TABLE IX. MALE FACTORS BY INDIRECT OBSERVATION

TEST	NO. OF CASES
Huhner	
normal	48
abnormal	56
Sperm	
normal	62
abnormal	61
Sperm in successful pregnancies	
normal	65%
Sperm in unsuccessful pregnancies	
normal	44%

The principle of tubal insufflation as devised by Rubin is an indispensable procedure in the study of infertility in the female. It is sometimes forgotten, however, that the apparatus demonstrates the presence or absence of patency throughout the entire reproductive tract, although Rubin has shown rather conclusively that the lesser fluctuations on a kymographic tracing are due to tubal peristalsis. In the 210 cases reviewed here, the "Rubin Test" was performed 306 times on 193 women. In the women who became pregnant, patency was demonstrated or achieved at the first trial in 67 per cent; in those who did not become pregnant, in 68 per cent. It was necessary to perform the test twice in 62 cases; in the pregnant women, patency was then demonstrated in 76 per cent of the cases, and in the nonpregnant in 71 per cent. These figures would seem to indicate about an equal incidence of the tubal factor in both groups of women. As shown in the following table, the test was repeated a varying number of times in a decreasing number of patients. Eventually, two patients received the test seven times each, one of these patients eventually became pregnant. In 35 cases occlusion was the final notation, although in many of them the test was performed only one time. Lipiodol studies were performed 17 times, and in the subsequently pregnant group demonstrated patency in four out of five cases. In one case the lipiodol was occluded, as were three Rubins, but pregnancy oc-

TABLE X. TUBAL INSUFFLATION AND LIPIODOL IN MECHANICAL OCCLUSION

TESTS	NO. OF CASES
Total Rubin tests	193
Total Rubin tests done	306 times
Total lipiodol tests	17
Patency first time, pregnant group	67%
Patency first time, nonpregnant group	68%
Rubin test twice	62
Rubin test 3 times	31
Rubin test 4 times	11
Rubin test 5 times	4
Rubin test 6 times	3
Rubin test 7 times	2
Finally occluded	35
Lipiodol occluded pregnant group	1
Lipiodol patent pregnant group	4
Total lipiodol pregnant group	5

curred anyway, clearly demonstrating the sometimes remote value of tubal insufflations and lipiodol injections. The lipiodol was occluded in 6 of 12 cases in the nonpregnant group.

### Endocrine Factors

Endocrine factors in infertility are demonstrated in an office study on the basis of: (1) history, (2) physical findings, (3) basal metabolic rate, (4) endometrial biopsy.

Nineteen cases complained of delayed onset of menstruation, the age 16 years or over being taken as a criterion; 29 cases described menstrual irregularities. Hirsutism of the masculine type, infantilism of the primary or secondary organs of reproduction, pelvic girdle fat distribution, prepubertal and pubertal obesity, rapid weight gain, and acne were observed in 26 cases. Fifty-five patients were overweight for height and body structure, 18 patients were underweight. In all, 61 per cent of the cases showed endocrine stigmas of which the majority were ordinary obesity. This would seem to indicate the group so favorably treated by thyroid. At any rate, the fat woman is definitely more often sterile than the thin or normal woman.

Fibromyomas may be endocrine in origin and in effect, or may be mechanical in effect. Probably they are both. These tumors were encountered in 11 cases, of which only one patient eventually became pregnant. The small, cystic ovary is difficult to diagnose by palpation alone. However, the condition was recorded in 17 cases; 29 per cent of the cases with cystic ovaries occurred in the group becoming pregnant. Frank ovarian cysts were found in 12 cases, two of which were subsequently shown to be endometrioma, one of these latter occurring in a patient subsequently pregnant.

The basal metabolic rate was determined in 125 cases. It was normal (minus 10 to plus 10) in 74 cases. Subclinical hypothyroidism (0 to minus 10) was not considered. It was below normal in 46 cases, although had the subclinical group been included here, the figure would be much higher. It was above normal in five cases. Thirty-six per cent of the cases upon whom the basal metabolism rate was done were, therefore, clinically hypothyroids. Again the

TABLE XI. MISCELLANEOUS ENDOCRINE FACTORS

TYPE	NO. OF CASES
Delayed onset	19
Irregularities	29
Stigmas	26
Obesity	55
Underweight	18
Total endocrine stigmas	61%
Fibromyomas	11
Pregnant	1
Cystic Ovaries	17
Pregnant	29%
Ovarian cysts	12
Endometrioma	2
Pregnant	1

TABLE XII. THE THYROID AS AN ENDOCRINE FACTOR

Total number of cases tested	125
Number of cases, basal metabolism rate normal	74
Number of cases, basal metabolism rate below normal	46 (36%)
Number of cases, basal metabolism rate above normal	5
Hypothyroids pregnant	30%

TABLE XIII. THE OVARIES AS AN ENDOCRINE FACTOR

TYPE	NO. OF CASES
Total biopsies	135
Ovulation positive	87
Endometrial hyperplasia	24
Endometrial hypoplasia	11
Endometrial infection	13
No ovulation but pregnancy	9

reason for the efficacy of thyroid in treatment is emphasized. Less than one-third of the cases of hypothyroidism became pregnant.

It is axiomatic that ovulation must occur if conception is to occur. We are fortunate in having ready access to the endometrium in which this event is reflected. We are in accord with the statement that an endometrial biopsy showing a failure to ovulate means only that the woman failed to ovulate during that particular cycle. Similarly, the typical secretory endometrium indicative of ovulation does not mean that the woman always ovulates. However, it cannot be denied that we will be right many more times than not if we assume that she ovulates regularly if the endometrium is secretory. Biopsies of the endometrium were obtained by the use of the aspiration curette in 135 cases. Ovulation was diagnosed in 87 of these, endometrial hyperplasia in 24 cases, endometrial hypoplasia in 11 cases, and infection in 13 cases. The conclusion that a single biopsy does not indicate ovulation during every cycle is confirmed by the fact that nine cases eventually becoming pregnant showed no evidence of ovulation. Our treatment with the gonadotropes was so infrequent and so poorly evaluated that we do not ascribe this occurrence to the effect of our therapy.

### Method of Treatment

In an attempt to overcome the various types of mechanical factors encountered in the infertility of this series, the following surgical procedures

were employed: cauterization of the cervix, 27 patients (13 of whom became pregnant); Hyams conization of the cervix, 7 patients (2 of whom became pregnant); modified Sturmdorf amputation of the cervix, 16 patients (6 of whom became pregnant); suspension of the uterus, 2 patients (none became pregnant); dilatation and curettage, 2 patients (one of which became pregnant); oophorectomy, 4 patients, of which 2 were for endometrioma, one for solid tumor of the ovary (one of whom diagnosed endometrioma became pregnant); dilatation of the cervix, 7 patients (3 of whom became pregnant). Plastic surgery to overcome stricturing of the introitus was performed one time, and this patient became pregnant. The production of an endometrial groove before expected ovulation in the manner described by Rock was done once, and the patient became pregnant immediately following. Other methods utilized in overcoming mechanical factors were: Smith-Hodge pessary, 12 patients (6 of whom became pregnant); knee-chest, 10 patients (5 pregnant); artificial insemination, 1 patient (no pregnancy). It must not be inferred from the above that we credit the procedure indicated for the pregnancies that occurred in this group. In all of these patients, other methods of treatment were also employed.

TABLE XIII. TREATMENT OF MECHANICAL FACTORS

PROCEDURE	NO. OF CASES	NO. PREGNANT
Cauterization of cervix	27	13
Hyams	7	2
Sturmdorf	16	6
Suspension	2	0
Curettage	2	1
Oophorectomy	4	
endometrioma	2	1
solid tumor	1	0
salpingo-oophoritis	1	0
Dilatation cervix	7	3
Vaginal plastic	1	1
Rock procedure	1	1
Smith-Hodge pessary	12	6
Knee-chest	10	5
Artificial insemination	1	0

TABLE XIV. TUBAL INSUFFLATION AS THERAPY

Times performed	113
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Tubal insufflation is both diagnostic and therapeutic; it is not possible to tell when it is the one and when it is the other. We have rather arbitrarily said that it should be considered as a treatment if used more than one time. This seems justified since the second, third, fourth, etc. Rubin tests were performed because the first showed excessively high pressures to establish patency or met with frank occlusion. On this basis, the procedure was used as treatment 113 times. There was one case in which the heavy oil, lipiodol, seems to have produced patency, although the x-ray did not show this and the Rubin test had been done three times previously.

With the exception of thyroid, none of the endocrines received a fair trial in our hands. Sixty-one cases received thyroid extract; 36 per cent of the cases

who received thyroid became pregnant and, of all the cases who became pregnant, 30 per cent received thyroid. We are convinced that this drug is an excellent one in the treatment of infertility. The estrogens, progesterones, and gonadotropes were used in 22 cases. Their use was essentially empirical and the results obtained, if any, cannot be evaluated. Vitamin E was used in 18 cases. We have no opinion regarding its efficacy.

TABLE XV. THE ENDOCRINES IN THERAPY

	NO. OF CASES	PREGNANT
Thyroid extract	61	36%
Steroids and gonadotropes	22	
Vitamin E	18	

Result of Treatment

We have a record of 73 pregnancies in this series of 210 cases (35 per cent). This total includes 53 normal, living babies (25 per cent). Nine pregnancies ended in abortions or miscarriages. One ended in a tubal pregnancy. Ten were recorded as pregnant with the outcome not indicated; seven of these are pregnant at this time so that the outcome must be awaited. At the time this paper is completed, our follow-up data has not been completed. It has been noted, however, that additional reports indicate about one successful pregnancy in each four cases, and we, therefore, do not anticipate that subsequent data will modify our statistics to any appreciable extent.

TABLE XVI. RESULT OF TREATMENT

	CASES	PER CENT
Pregnancies	73	35
Living babies	53	25
Abortions and miscarriages	9	
Ectopic	1	
No record of outcome	3	
Now pregnant	7	

Summary and Conclusion

We can now answer the question asked in the first part of this paper. One of each four women who complain of infertility will succeed in producing a normal, viable offspring under treatment as we employ it.

The longer the woman accepts her infertility without treatment, the less success will be had with any efforts to correct it.

Cervical erosion, infection, and general pathology were a surprisingly frequent finding in this group.

Abnormalities of the sperm occurred in 50 per cent of the male partners.

Tubal insufflation is of outstanding value both diagnostically and therapeutically.

Endometrial biopsy is diagnostically essential, but, with the exception of thyroid, the endocrines were poorly evaluated.

Thyroid is a valuable drug in the treatment of infertility.

## COEXISTING CANCER OF THE OVARY AND FUNDUS\*

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THE purpose of this paper is to record a case of cancer of the ovary and fundus coexisting and to consider available relative information.

This patient was seen first May 5, 1939. She was 47 years old and had been married twenty-four years, with one child, aged 23 years. Her chief complaint was irregular bleeding for the past two years. This irregularity was described as prolonged periods, practically continuous bleeding. Her menstrual history had been normal until two years ago. There had been no operations, but labor was difficult, requiring forceps. The patient stated that she was never well after labor. Examination showed extensive cystic degeneration of the cervix with large erosions. The pelvis was filled with a large irregular mass which extended nearly to the navel. The provisional diagnosis was extensive cervicitis and multiple fibroids of the uterus. The cervical and endometrial biopsy was done on May 9, 1939. After passing sound into the cervix, a considerable amount of material was expelled, which was apparently carcinoma, and microscopic study showed it to be adenocarcinoma. The biopsy from the cervix showed cervicitis only. This examination was followed by high temperature, chills, and other evidences of infection. After several weeks, when the patient's condition permitted, she was given deep x-ray therapy. After two and one-half months' hospitalization, the patient was discharged and her condition was found to be essentially the same, except slight mobility of the tumor. The bleeding had been controlled, but pain was severe. She was offered surgery at this time, though the prospects seemed most discouraging. An operation was performed on Sept. 21, 1939. At this time, the mass was most prominent in the right pelvis. The mass, which still extended nearly to the navel, was fairly movable, although the motion was limited. A low midline incision was made, and the principal mass was found to be derived from the right ovary. This mass was covered by many loops of intestines, ileum, and sigmoid, which were adherent to the mass by inflammatory adhesions. The uterus was pushed to the left, and was of normal size. The left tube and ovary were adherent to the left pelvic wall and broad ligament by fine inflammatory adhesions. The left ovary was degenerated and atrophic. The liver was palpated, no nodules were found, and there were no palpable retroperitoneal glands. The adhesions about the right ovarian mass were separated with great care, but, in separating the adhesions, the mass was ruptured and was found to contain a large amount of thick yellow pus. This pus was apparently coming from the degenerating ovarian malignancy. After the mass had been completely freed and removed, the left tube and ovary were likewise freed. Bilateral salpingo-oophorectomy and panhysterectomy were done. The cancerous growth was separated from the coils of intestine to which it closely adhered. The postoperative diagnosis was "Carcinoma of the right ovary, pus formation and degeneration of the right ovary, partial intestinal obstruction, inflammatory adhesions, carcinoma of the fundus." The laboratory diagnosis was, "Adenocarcinoma and multilocular cystadenoma of one ovary; adenocarcinoma of the uterus; chronic endocervicitis; chronic salpingitis, bilateral."

\*Read before the meeting of the South Atlantic Association of Obstetricians and Gynecologists, Feb. 16, 1946.

## Comment

It is noted that this patient's symptoms of irregular bleeding continued over a period of two years before any advice was sought by the patient. This is surprising, as the patient's mother died of cancer. This patient is well after six years and shows no evidence of cancer in her pelvis or anywhere else. It is remarkable that a cancer so advanced should have even a six-year cure by any means whatever. There was nothing unusual about the treatment, which was x-ray followed by panhysterectomy and bilateral oophorectomy and salpingectomy. The tumor was obviously partially radiosensitive, and this effect, no doubt, rendered the operation and the cure possible. Ewing suggested that spontaneous regression of these tumors occasionally occurs. Meigs attributes the regression of papillary peritoneal implants following bilateral oophorectomy to the removal of some of the source of estrogen production. The favorable effects on carcinoma of the prostate following removal of the testes has been observed by some. It is possible that all of these influences may have been helpful and aided in the recovery of this patient. We know that there will not be many cases which will recover under the circumstances, but there is some encouragement not to leave such cases to die without making any effort to cure them.

This condition, cancer of the ovary and fundus of the uterus separately, seems to be a relatively rare condition. However, Novak<sup>6</sup> found seven such cases in a series of 147 cases of adenocarcinoma of the corpus. The one which I report is the only one found in a series of 69 cases of adenocarcinoma of the fundus treated at the Norfolk General Hospital during a period of ten years. I have recently found reports of four other cases occurring in the literature since 1920. One of these<sup>1</sup> was obviously a Krukenburg tumor which involved both ovaries and the uterus, probably not a very uncommon occurrence in a Krukenburg tumor. It is quite possible that this search is hampered to some extent by nomenclature, as there are probably others which have been classified differently. Of course, in the latter stages of extensive cancer of the pelvis it might often be seen. A very brief abstract of these cases follows:

CASE 1.<sup>2</sup>—Patient was 17 years of age. Bilateral adenocarcinoma of the ovary and of the neck of the fundus; histologic structures identical in all three locations. The author assumes the pathogenetic probability here was that the ovary was the original site, and the cells were picked up by the fimbriated end of the tube and carried to the endometrium. The whole tumor mass here extended above the umbilicus. At operation, both tubes and ovaries and complete hysterectomy were done. The patient was dismissed in good health on the twenty-eighth day. There is no note on the future.

CASE 2.<sup>3</sup>—This patient was 63 years old. The symptoms were the usual—pain, bleeding, and mass. Laparotomy revealed cystic tumor of the right ovary about the size of a fist with peritoneal extension. Subtotal hysterectomy was done. The uterus was opened at the time of operation and showed obvious cancer. Report of microscopic study was "cancer of the ovary and fundus." Patient died twelve days after operation.

CASE 3.<sup>4</sup>—This patient was 50 years of age. Symptoms were bleeding, pain, and a mass in the lower abdomen. Laparotomy revealed a nodular uterus and a large cystic mass on the left side. Hysterectomy and removal of the cyst was done. Study of the tissue showed cancer in the ovary and the uterus. Patient died a few months later from extension of growth.

Alfieri,<sup>5</sup> in his monograph on the pathogenesis, gives four distinct combinations of the pathogenetic possibilities of the two carcimatous tumors:

1. Both uterine and ovarian carcinoma are primary and independent.



2. The ovarian carcinoma is primary and the uterine secondary.
3. The uterine carcinoma is primary and that of the ovary secondary.
4. Both neoplasias are secondary to one originating outside of the sexual apparatus.

As to whether they originate in the ovary or the uterus more frequently, there is some difference of opinion. Novak expressed the belief that they commonly originate in the uterus and are transmitted through the lymphatics to the ovary. Since cancer is more commonly transmitted through the lymphatics, there is much evidence in the favor of this plan.

Sampson's theory that the regurgitated menstrual blood carries implants of either endometrial tissue or cancer to the ovary or elsewhere is a possible explanation. In my case, the tumor of the ovary was far advanced and extensive, whereas the uterus was of practically normal size, and the endometrium only was involved. Under these circumstances, it would seem reasonable to suppose that the ovary was the original site of the tumor. It would also seem a possibility that the cells were picked up by the fimbria of the tube and carried to the endometrium. Of course, the lymphatics are also a possibility. The fact that the type of cancer cells in both tumors are identical in both ovary and uterus would lead one to believe that they were not of independent origin.

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## PHYSIOLOGY OF LABOR\*

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IN THE physiology of labor much importance should be placed upon the muscular action of the uterus and its results in expulsion of a living fetus. As a prelude it may be stated that nature has developed an enormous store of checks and balances, many of which are only surmised and some may be of the utmost complexity. Among the latter are the labor functions of acetylcholine, cholinesterase, epinephrine, posterior pituitary extract, histamine, and sympathetic and parasympathetic nervous control, as well as the various endocrine functions in health and in disease. In addition, the actions of the myriads of possible chemicals upon these complex processes is practically a closed book, but also an inviting field for investigation. These are all subjects for the most productive of research, but they require energetic prosecution by means of obstetricians, biochemists, pathologists, physiologists, and pharmacologists. Two of the most intriguing phases of physiology of labor are the cause of the onset of labor and the train of events that leads to eclampsia. Since the early work of Schatz<sup>1</sup> in 1871 to 1872, intrauterine pressure studies have been made by Hensen,<sup>2</sup> Rucker,<sup>3</sup> Bourne and Burn,<sup>4</sup> Wielock,<sup>5</sup> Salerno,<sup>6</sup> Bickers,<sup>9</sup> and Moir,<sup>10</sup> using balloons placed into the uterine cavity before, during, or after labor.

During the past nine years, Woodbury<sup>7, 11</sup> and associates, working with obstetrical patients in the University Hospital, have obtained numerous prolonged continuous records made with the Hamilton closed fluid differential manometer. By this means simultaneous continuous exact pressure readings are optically recorded of any of the following: (a) intrauterine pressure above the fetal head, or (b) below the fetal head, (c) the stomach pressure, (d) the maternal intra-arterial pressure, (e) intravenous pressure. Besides the simultaneous record of these individual pressures, a record may be made of the differential between any two.

Throughout pregnancy there are the Braxton-Hicks contractions causing minor changes in the pressure intermittently every two minutes or so, enough to maintain some flow of blood in the intervillous placental spaces. These probably serve to oxygenate the uterus and the fetal blood. At the onset of labor these contraction waves acquire greater amplitude, and the intrauterine pressure rises from a tone pressure of 5 mm. Hg to several times that amount, so that there occurs a sensation of labor pain. This pain sensation arises at various pressures from 25 to 35 mm. Hg, depending upon the irritability of the patient. During normal labor then, in the first stage, the intrauterine pressure rises slowly with each contraction to a peak of 35 to 60 mm. Hg, and then equally slowly falls to the uterine tone pressure of 5 to 8 mm. Hg. The length of the palpable contraction during which the uterus is felt to be firmly

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contracted is approximately forty seconds and of the interval between contractions, two to five or more minutes. In the second stage after full dilatation of the cervix, the apex of the contraction wave usually is higher than in the first stage, and may rise to a maximum of 110 mm. Hg and the "inter-contraction" tone remains higher at 10 to 12 mm. Hg, about twice what it was in the first stage. During the second stage the more or less voluntary contraction of the abdominal muscles practically doubles the effective intra-uterine pressure so that the combined pressures caused by the contraction of the uterine muscle and of the abdominal muscles may reach 260 mm. Hg (which was the highest recorded). The effective pressure in expelling the fetus whose average presenting head diameter was 9 cm., calculated from the uterine contractions, was between 8 and 18 pounds. The abdominal muscles increased the expulsive forces to 22 to 46 pounds. These were all in well-developed sturdy primiparas.

Further use of the differential manometer revealed that the pressure within the placenta is such that the maternal blood is being squeezed out during the uterine contraction, usually into the vena cava, but in one case, actually into the aorta also, for the intrauterine pressure was higher than the maternal arterial pressure. The effect is naturally greater if the maternal blood pressure is low. This action causes approximately a pint of blood to be thrown back upon the maternal systemic circulation at each labor contraction, raising the venous pressure approximately 10 mm. Hg, and may be a factor in the danger of labor in decompensating cardiac patients. There is a slight increase in arterial pressure during a labor contraction, greatly augmented if there is coincident "bearing down" by abdominal muscular action.

*Physiologic Effect Upon the Fetus.*—During the first stage of labor, the pressure changes equally affect both the entire fetus, as well as its placental circulation, therefore it is practically without damage unless something obstructs the oxygen and the metabolites' supply to the fetal blood. However, during normal labor there is probably a better exchange of oxygen and metabolites from the maternal blood than previously, because of the increased maternal blood flow due to the heartlike action of the uterus with its contraction as systole and its prolonged interval with low muscular tone as diastole. In the second stage only is there greater pressure above the fetal head than below, but this again is intermittent and allows for adequate oxygenation of the fetal blood.

*Abnormal Labor.*—During the years of study there were not infrequently patients found who had abnormal physiology of labor. These, as a rule, were the so-called dystocia dystrophy type well described by DeLee, Horner, and others. It was also found that similar physiologic alterations of normal labor occurred in practically all parturients who had abnormal labor, especially in those who had inadequate therapy during labor or in prolonged obstructed labor. Some of the factors influencing the production of this altered labor were found, and, coincidentally, some measures of prevention or correction even after several days of labor were ascertained.

In dystocia-dystrophia syndrome, the patient often has the characteristics of pituitary dysfunction of increased weight, short stature, or stocky build, with relatively long torso and short thighs. Her fingers are short and stubby. She may conceive with difficulty, and when pregnant, if she doesn't abort, often has a tendency to go "over term" and then enter a prolonged and tedious labor. Besides, she more often is subject to abnormal weight increases with attendant inclination to toxemias of pregnancy. In these the abnormality of labor is generally not due to alterations in the pelvic structures as has been thought to be the case. A study of the pelvis by exact roentgen-ray measurements in eight cases revealed that seven were gynecoid in type with moderate contraction of the anteroposterior diameter below 10 cm. in two, slight contraction (10 to 11 cm.) in three, large gynecoid pelvis in one. The eighth, a Negro woman, had a contracted android type of pelvis. Since these observations were made, many other cases have been encountered, and in not one was there found coincident fetopelvic disproportion enough to preclude vaginal delivery. The abnormality of labor then is due mainly to altered physiology of the uterine contractions. Moreover, this same altered physiology has been found to be present in almost all other cases of prolonged labor, and its onset is earlier if the labor is poorly managed. The characteristics of these abnormal labor states appear in the continuous record of the intrauterine pressures. First, the labor contraction waves are shorter, more peaked, and of variable amplitude as well as variable intervals of recurrence; second, and of such importance as to be almost pathognomonic, the intercontraction tone remains much above the normal of 5 to 8 mm. in the first stage of normal labor, and of 10 to 12 mm. in the second stage. In the dystocia dystrophy type of labor this tone may rise to 15 to 18 mm. Hg or more. This, if long continued, causes disastrous results, not only to the fetus, which becomes hypoxic, but also to the mother, wearing her out by fruitless nagging pain which, because of the lack of blood and oxygen to the uterine wall, fails in enough force to dilate the cervix and expel the fetus.

All experienced obstetricians have repeatedly seen just such cases, although they may not have recognized the crucial fact that the uterus remained unusually firm between "pains" to such an extent that in some instances the patient's sensation of pain was continuous. Since the high intercontraction tone seemed to be the most characteristic finding in these cases, much interest was taken to ascertain the effect of various anesthetic drugs upon them. Only one was found which had the ability to abolish in most cases the abnormal contractions with the intervening elevated intrauterine pressure. This was morphine. The other anesthetics and barbiturates may be of value in preventing the occurrence of this condition, but are of little or no influence in curbing the condition once it begins. The effects of the anesthetics upon normal labor contractions are revealed in tracings. It was also found that, while morphine in adequate dosage, usually at least  $\frac{1}{4}$  grain subcutaneously, was effective in abolishing abnormal labor contractions and of relieving the uterine tension between contractions, that it had no effect upon normal labor contractions after they have been definitely established. In addition, it frequently changed

abnormal labor into normal labor in which the cervix, heretofore stationary in dilation, soon began to dilate, and within in a few hours (often surprisingly few) the fetus delivered spontaneously. Besides, all other anesthetics and hypnotics, as usually used, were found to have little adverse effect upon the normally acting uterus. There was a small percentage of cases in which morphine administration was not followed by prompt relaxation of the uterus, and in one instance in which the uterine tone between contractions was estimated by palpation to be at least 35 mm.,  $\frac{1}{4}$  grain morphine subcutaneously had no appreciable effect in relaxing the uterus, and the fetus continued to be in poor condition (pulse rate of 70), and in the course of one hour the heart rate gradually became slower and ceased entirely. This was not a condition of a contraction ring, because the uterus continued to have intermittent contractions and spontaneously expelled the dead fetus twelve hours later, in spite of abnormally high tone between contractions. It may be that a larger dose of morphine or deep anesthesia by another agent would have been effective. Or this may have been of different origin than usual, and possibly epinephrine, magnesium, or some other drug may be found to be more effective than morphine in a few instances.

*Other Causes of Dystocia Dystrophy Syndrome Type of Labor.*—Besides the constitutional type of patient subject to dystocia dystrophy syndrome, it has been discovered that any patient in labor may be thrown into similar abnormal type of labor by repeated administration of oxytocic drugs, pituitrin, and ergot preparations. The intercontraction tone gradually rises with repeated doses of the drugs until complete tetany exists.

It was found that in certain cases of toxemia with hypertension, large weight gain, edema, often associated with dehydration and anemia, there may be development of this abnormal type of labor. In several instances it was found in otherwise normal and well-nourished women with adequate pelvic canals who were markedly anemic. It also developed in several women with moderate to severe grades of fetopelvic disproportion, as determined by exact x-ray studies. These, as a rule, were those whose labor management was not ideal according to standards elsewhere outlined.

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## THE USE OF PENICILLIN IN REPAIR OF COMPLETE PERINEAL LACERATIONS\*

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I WISH to report four cases of complete perineal laceration, operated upon since June, 1945, in which penicillin was given after the operation as a routine procedure. They all had the same preoperative preparation, and the same type of operation was used. The preoperative preparation included a general physical examination, and special attention was given to correcting any existing anemia or cervical erosion. One week before the operation, 60 grains of sulfasuxidine were given daily. A sulfathiazole suppository was inserted in the vagina at bedtime, and a douche of one-half cup of vinegar to a quart of water was used the next morning. Two days before the patients were admitted to the hospital, a mild laxative was given, and they were also put on a non-residue diet. The patients were admitted in the evening, and the operations were performed the following morning.

In all these cases, there was an absence of a part of the anterior rectal wall. In one case there was very little perineal tissue on the right side of the vagina. Tincture of merthiolate was used to prepare the operative field. A transverse incision was made on the posterior vaginal wall, going high enough up in the vagina to make a flap to be used as the anterior rectal wall. This transverse incision across the vagina was curved to the vaginal outlet, and dissected very carefully so as not to buttonhole it, and also to leave enough tissue on the flap to give it an adequate blood supply. The dissection of this flap was stopped just at the junction of the rectal and vaginal mucosa. The vaginal mucosa was dissected forward to give a flap to be used in the perineorrhaphy. The sphincter muscle was then isolated and brought together across the outer flap of the posterior vaginal wall and sutured with number one chromic catgut. It was then reinforced by suturing the adjoining fascia over this flap. Care was taken that there was no tension in bringing the muscles together. The next step was to suture the vaginal flap to the skin edge and follow with the usual perineorrhaphy.

Postoperatively, the patient was given a nonresidue diet for four days, and 10,000 units of penicillin in the muscle every three hours. On the fourth postoperative day, one-half ounce of mineral oil was given three times a day, and on the next day 2 ounces of mineral oil were injected in the rectum through a catheter. If there were no results from the preceding treatment, the patient was given a mild laxative that night.

### Case Reports

CASE 1.—Mrs. W. T. D., aged 28 years, was operated upon on June 25, 1945. She had had one pregnancy four years ago. Labor had been difficult and forceps were used. She was left with a complete laceration, and part of the right perineal body was gone. In this case, I dissected where the sphincter was supposed to be, and obtained what I hoped was the sphincter, but was not sure of it. I had to pull the left side of the perineum over and sew it to the fascia of the pubic bone. This case was so bad, and since penicillin was being used for everything else, I decided to try it on her. She was in the hospital for fourteen days,

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and spiked a temperature to 100° F. for ten days, with the highest temperature being 100.4° F. for one day. On the ninth postoperative day, after her bowels had been moving through the rectum, some feces were found in the vagina. On pelvic examination, the perineum was found to be intact and in good repair. Rectally, there was a defect where the vaginal flap had been sewed to the skin. Potassium permanganate douches were given. After they had been used for two days, the solution returned clear, and no feces have been found in the vagina since. When the patient had her first pelvic check-up, a granulating area was found on the anterior rectal wall near the skin edge. This was painted several times with silver nitrate. She now has a good perineal body, has good control of her bowels, but at times poor control of gas. The latter is gradually improving.

CASE 2.—Mrs. D. W., aged 61 years, who was operated upon on Oct. 8, 1945, had had four children, the youngest 20 years old. She had a complete perineal laceration with her last child. She had a fungus infection around the rectum. She was in the hospital for fourteen days following the operation. Her temperature ran around 100° F. for six days, with one day a maximum of 100.4° F. She passed a small amount of blood on the tenth day. A pelvic and rectal examination showed a good perineum. She has good control now of both bowels and gas.

CASE 3.—Mrs. B. M., aged 41 years, who has four children, was operated upon Nov. 2, 1945. She had had no bowel control for fourteen years. This patient, in addition to the perineal repair, had a suspension, ligation of tubes, and an appendectomy. She was in the hospital for ten days and had temperature over 99° F. for three days, the highest being 100.2° F. for one day. She now has good control of her bowels and gas, and has a good perineum.

CASE 4.—Mrs. A. W., aged 45 years, who has 10 children, was operated upon Nov. 26, 1945. She had had no control of her bowels since the first baby was born twenty-four years ago. She was told that if she was repaired, she could have no more children. She was in the hospital ten days. Her highest temperature was 99.2° F. on one day. She now has a good perineum and good control of both bowels and gas.

### Summary

The four patients cited stayed in the hospital an average of twelve days. The highest temperature charted was 100.4° F. One patient had a fair result, three had excellent results. The postoperative use of penicillin in complete perineal repair seemed a definite advantage.

## LATE POSTPARTUM HEMORRHAGE\*

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AS DEFINED in this paper, late postpartum hemorrhage indicates prolonged or excessive uterine bleeding beginning after the first day following delivery. The attempts of other authors (Robertson and Kleinwachter<sup>1</sup>) to extend the interval to reach from the first to the twenty-eighth day postpartum, and to subgroup an early and later type, offer no advantages. The frequency of l.p.p.h.† is difficult to ascertain because of the paucity of reports. Williams<sup>13</sup> and DeLee<sup>14</sup> make only brief mention of the subject, while Davis and Schuman omit any reference to its occurrence. In American literature only one report by N. H. Williams appeared on this subject since 1939.<sup>12</sup> Chiare and Robertson<sup>1</sup> record an incidence of 1:250 to 1:300 for the late group of postpartum hemorrhage from all causes. This paper, however, excludes cases of l.p.p.h. from ruptured varices or atheromatous vessels, from coincidental tumors (fibroids or carcinoma), from lacerations (cervical, perineal, and vulval), and from uterine inversion.

It deals with late postpartum bleeding due to: (1) Retained placental fragments. Focal placental accreta is not recorded in this group, but there is one case of a retained succenturiate lobe. The remaining cases are fragments derived from normal placentas. (2) Uterine abnormalities in involution of the placental site. (3) Uterine abnormalities in retention and separation of the decidua vera.

### Retained Placental Fragments

Stadfeldt (quoted by Siegel<sup>9</sup>) found seven cases of retained placental fragments in 70 autopsies performed upon postpartum women. The cause of death, however, was not stated. At the Brooklyn Jewish Hospital there were 32 cases of retained placental fragments after 32,155 deliveries, an incidence of 1 to 1,005 cases. There were five additional cases confined in other institutions, making a total of 37 cases of this group encountered between Jan. 1, 1934, and Sept. 1, 1944. While generally agreed that true Credé maneuver or manual removal of the placenta are predisposing causes in retention of placental fragments, the hurried conduct of the third stage of labor can be a paramount factor. It is, therefore, necessary to record our management of the third stage of labor. Delivery is conducted under gas-oxygen-ether anesthesia. At the birth of the child,  $\frac{1}{2}$  c.c. of pituitrin is administered intramuscularly, and anesthesia is lightened. With rise in the height of the fundus, or descent of the cord, a modified Credé is performed, and the spontaneously separated placenta is expressed. One c.c. of ergotrate is then administered intramuscularly, and the uterus is carried well out of the pelvis. The placenta and membranes are then inspected. A course of  $\frac{1}{320}$  grain ergotrate tablets every four hours for

\*Read at a meeting of the Brooklyn Gynecological Society, May 3, 1946.

†Late postpartum hemorrhage, elsewhere designated by l.p.p.h.



six doses is routinely administered during the first day post partum. It must be emphasized at this point that detection of a missing fragment smaller than a cotyledon is not easy if the placenta has been compressed or traumatized in its delivery. Remaining in situ a retained fragment undergoes one of the following courses: (a) spontaneous expulsion (4 cases); (b) operative removal after one or more episodes of bleeding (31 cases); and (c) enmeshment or polyp formation (2 cases).

*A. Spontaneous Expulsion of a Retained Placental Fragment.*—It may be complete or partial, and four such cases have been encountered. Reduction in the size of the uterus during its involution causes separation of the attached fragment. Underlying sinusoids and veins are opened, and intrauterine bleeding follows. Muscle contractions which may ensue help further to separate the retained fragment and favor its expulsion from the uterine cavity. The clinical manifestations of this group are abstracted below.

CASE 1.—(AA24,273), gravida ii, para i. The first pregnancy terminated in early complete spontaneous abortion. The current pregnancy continued to term. Labor was without incident, and the third stage was uneventful. The first episode of slight bleeding occurred on the fourth day after delivery and, in spite of a course of ergotrate, staining continued after discharge on the twelfth postpartum day. On the thirty-fifth postpartum day, active bleeding associated with uterine cramps resulted in the spontaneous expulsion of a placental fragment measuring 4 by 3 by  $\frac{1}{2}$  cm. All bleeding then ceased.

CASE 2.—(AA35,632) A primipara at term delivered without incident. The placenta was retained for ninety minutes without bleeding. A true Credé maneuver was then performed under anesthesia, and the placenta was delivered, apparently intact. A febrile postpartum course was attributed to an infected perineum. On the tenth day postpartum, the patient bled and, in spite of absence of cramps, a small fragment of placenta was spontaneously expelled. On the sixteenth postpartum day a second hemorrhage followed. This did not respond to ergotrate, and on the seventeenth postpartum day the continued bleeding necessitated curettage. A small residual placental fragment was obtained. The uterus and vagina were then packed and a transfusion of 500 c.c. was given. The postoperative course was uneventful and all bleeding ceased.

CASE 3.—(AA37,476) A para ii, gravida ii delivered without incident at term. The placenta separated spontaneously in five minutes and was expressed seemingly intact. There was moderate bleeding on the third postpartum day. A course of ergotrate was given, resulting in expulsion of a small fragment 3 by 2 by 1 cm. The low grade temperature of 100.6° F. which had continued from the first postpartum day then returned to normal.

CASE 4.—(AA196,724) A primipara at term delivered without incident. The placenta separated spontaneously after twenty minutes and was expressed, supposedly intact. On the second postpartum day, there was moderate bleeding associated with passage of a placental fragment, 2 by 1 by  $1\frac{1}{2}$  cm. There were no cramps. The temperature remained elevated to the fourth postpartum day. Microscopically, the tissue fragment was free from infection.

*B. Retained Placental Fragments With Bleeding, Requiring Surgical Intervention.*—

1. *Afebrile:* Of 24 patients comprising this group, 14 were primiparas and 10 were multiparas. Labor was normal in 12 patients. Eight patients were

TABLE I. RETAINED PLACENTAL FRAGMENTS REQUIRING INTERVENTION

		AFEBRILE	FEBRILE
Mode of Delivery	Total cases	24	7
	Primiparas	14	4
	Multiparas	10	3
	Spontaneous	12	3
	Low forceps	7	0
	Midforceps	1	2
	Breech	1	1
Third Stage	Version	1 (twins)	0
	Other hospital	2	1
	Home	1	0
	Average length	8 min.	19 min.
	Expression	20	5
	Credé	1	0
	Manual removal	0	1

TABLE II. CLINICAL FINDINGS IN RETAINED PLACENTAL FRAGMENTS REQUIRING INTERVENTION

		AFEBRILE	FEBRILE
Onset of Bleeding in Days	1- 5	5	1
	6-10	13	1
	11-15	4	1
	16-20	1	3
	21-25	1	0
	26-30	0	1
Repeated Episodes	0	13	3
	1	2	1
	2	7	1
	3	0	1
	4	2	1
Clinical State	Lochia foul	0	4
	Abdominal cramps	5	1
	No shock	10	2
	Mild shock	4	1
Cervix	Severe shock	10	4
	Patulous	24	6
	Not stated	0	1
Uterine Subinvolution	Mild	4	0
	Moderate	14	4
	Marked	5	2
	Not stated	1	1

delivered by forceps. One breech required manual aid. The second child of a twin pregnancy was delivered by version and extraction. In three cases confined elsewhere the nature of delivery was not known. The third stage was normal in 20 patients, and one required a true Credé maneuver (Table I). The universal symptom of retained placental fragments is abnormal vaginal bleeding. In 18 of 24 cases it appeared within the first ten days following delivery. Most commonly, however, it appeared between the sixth and tenth day post partum (Table II). In the remaining six cases bleeding occurred between the eleventh and twenty-fifth postpartum day. Multiple episodes of varying intensity occurred in most instances. Although the amount of bleeding could not be accurately determined, its extent was in a measure indicated by the systemic condition of the patient. Shock (systolic blood pressure below 100, pulse above 100, pallor, cold skin) in varying degree was present in 14 cases. Of 10 cases in severe shock,

eight reached this status while under conservative medical routine. Abdominal cramps referred to the lower central segment were noted in only five instances. It is our impression that this symptom was associated only with large placental fragments. The lochia was seemingly normal in all patients before the advent of bleeding.

The clinical findings of the uterus cannot adequately be interpreted. Although all uteri were noted as subinvolved (Table II), accurate mensuration by a calibrated uterine sound, or measurement of the height of the fundus above the symphysis was not employed. It must be noted, however, that distention of the uterine cavity by blood clots would, in a measure, invalidate such findings. Upon examination, the cervix was patulous in all cases. Since this is a normal finding up to the twelfth postpartum day, the value of a patent cervix as a diagnostic aid would apply only to later cases. Thus, in nine cases curetted between the fifteenth and twenty-sixth days postpartum, respectively, a patent internal os was noted in each instance.

TABLE III. THERAPY IN RETAINED PLACENTAL FRAGMENTS

		AFEBRILE	FEBRILE
Medical	Not used	12	2
	Unsuccessful	12	5
Surgical	Curettage	16	4
	Curettage and pack	1	2
	Curage	2	0
	Curage, sponge stick and curettage	5	1
Location of placental fragments	Anterior	4	2
	Posterior	2	1
	Fundus	4	0
	Not stated	14	4
Transfusions	Preoperative	5	2
	Postoperative	5	2
	Pre- and Postoperative	1	1
Pathologic report	Infected	9	3
	Not infected	15	4
Postoperative course	Afebrile	18	2
	Febrile	6	5
	Sulfonamides used	6	2

2. *Febrile*: The febrile group of "retained placental fragment patients" is difficult to define. Elevation in temperature alone does not exclude infection in some other focus (e.g., infected perineum). Exudate of neutrophiles in curetted decidua is a physiologic finding up to the tenth postpartum day. Bacteriologic cultures are difficult to evaluate, for pathogens and nonpathogens can be found in the uterus by aspiration culture after the second postpartum day, even in women free from a morbid course. Blood counts and sedimentation rates, too, are physiologically altered in the puerperium. The presence of neutrophiles within the stroma of the retained villi is sure proof of infection; yet, even in the afebrile group, such fragments were recovered and designated as "infected placental tissue" (Table III). Reversely, too, in the febrile group, only three of seven placentas were reported as infected. It is evident that myometritis could not be detected from curetted material. We

define, therefore, as febrile those cases with an elevated temperature of 100.4° F. or above, occurring after the first postpartum day, and in which any other demonstrable focus of infection is lacking.

There were seven patients in this group, four primiparas and three multiparas (Table I). Three were delivered spontaneously and two by forceps. One breech required manual aid. The nature of delivery was unknown in the patient delivered at another hospital. The average length of the third stage was nineteen minutes in this group, compared to eight minutes in the afebrile group. One patient required manual removal of the placenta after one hour (Table I). The symptomatology was essentially the same as in the afebrile group, and requires no further comment. The onset of the bleeding, however, occurred somewhat later, for only two of the seven cases bled prior to the tenth postpartum day (Table II). In four other cases the initial episode of bleeding occurred after the sixteenth postpartum day. This may be explained by delayed uterine involution due to coincidental infection of the muscle wall. Repeated episodes of bleeding occurred in four of seven cases. The lochia was foul in four of seven cases prior to onset of bleeding. The clinical status of these patients was, as in the preceding group, the best gauge of the severity of blood loss. In this group five of the seven cases exhibited mild to severe shock. The longest preoperative febrile course was nineteen days, with temperature as high as 105° F.; the shortest was five days, with temperature of 103° F. In six of the seven cases wherein the preoperative and operative findings are completely recorded, it was found that the cervixes were all patulous and the uteri subinvolved. The finding of a patulous cervix in infected cases is of some diagnostic import, for onset of bleeding occurs more frequently after the twelfth day postpartum. Tenderness of the uterus upon abdominal or bimanual examination was not noted. Fortunately, the metrorrhagic form of puerperal sepsis as described by Couvelaire was not encountered.

*C. Polyp Formation of the Retained Placental Fragment (2 Cases).—*A retained placental fragment is occasionally transformed into a polyp. It is the result of repeated and incomplete attempts at separation, during which blood is deposited upon the surface of the fragment. Coagulation follows, resulting in the formation of a hemorrhagic mass protruding into the uterine cavity. As a rule, it is of moderate size, and more or less conforms to the size and contour of the cavity. Occasionally it may project through the cervix into the vagina, where it can mask as cancer of the cervix. On gross section, layers of blood and fibrin are adherent to the superior and lateral aspects of the polyp, while its base is separated from the muscle layer by decidua basalis. Microscopically, nutrition of the villi is surprisingly long preserved, but normal forms are intermingled with others in varied stages of necrosis. While the identity of a preserved placental polyp is easily established on palpation of the uterine cavity, those fragmented by curette or curettage often escape detection, especially if intervention follows prior to their hardening and firm attachment to the uterine wall. It may well be that some of the cases reported as retained placental fragments actually belong to this group.

The clinical manifestations of a placental polyp and the physical findings are essentially similar to those of retained placental fragments. Bleeding is more prolonged, or presents recurrent episodes of varied severity. Pain as a rule is lacking. Poor muscle tone may be the cause of prolonged retention of the fragment. To emphasize the clinical characters of placental polypi, the two cases encountered are briefly summarized.

CASE 1.—Mrs. B. G., aged 27 years, a primipara, was delivered normally at term in another hospital, seven months prior to admission. The early postpartum period was normal. About five weeks after confinement the patient supposedly had her first menses. The flow, however, lasted two weeks and was profuse. It soon recurred and continued intermittently for almost six months. Upon admission the uterus was found enlarged, subinvolved, and soft. Curettage yielded large hemorrhagic fragments of a traumatized placental polyp. The postoperative course was uneventful.

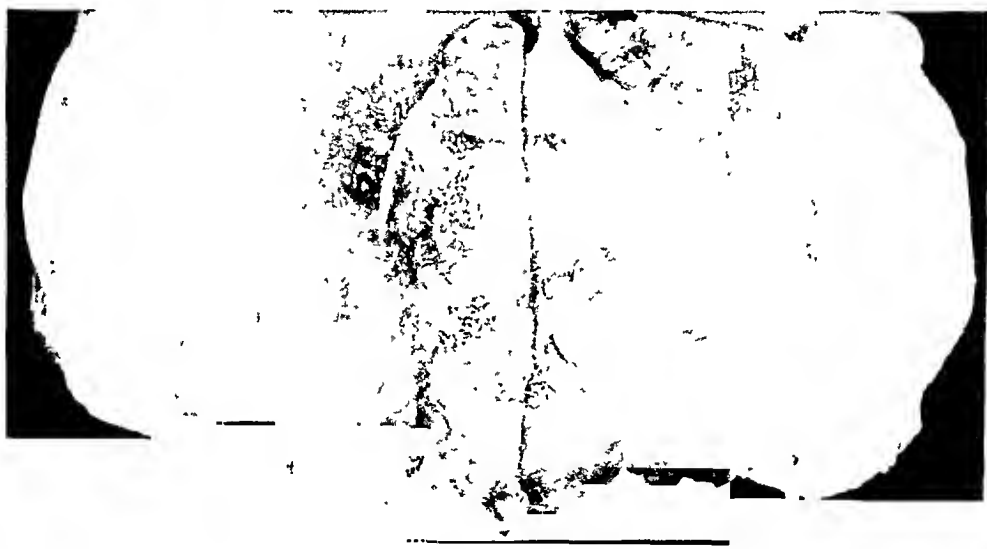


Fig. 1.—The placental polyp is centrally located on the posterior wall of the opened uterus. The external surface is relatively smooth but focally hemorrhagic. The base is attached high in the fundus. The apex of the polypoid mass projects below the level of transection.

CASE 2.—Mrs. R. S., aged 27 years, para ii, gravida ii. The first pregnancy and labor were without incident. The current second delivery was uneventful until the thirteenth postpartum day, when profuse vaginal hemorrhage occurred. The uterus, which extended for three fingerbreadths above the symphysis, was packed with plain and iodoform gauze, and intravenous glucose in saline was administered. After removal of the packing on the following day, a second profuse hemorrhage followed. Curettage yielded only moderate amounts of placental tissue. The uterine cavity and vagina were again packed, and a transfusion of 1,000 c.c. of blood was administered. The patient was discharged on the twenty-third postpartum day, only to be readmitted on the same day because of recurrence of profuse hemorrhage. A blood transfusion of 1,000 c.c. was immediately necessary. A fourth recurrent hemorrhage on the twenty-fifth postpartum day led to a supracervical hysterectomy. The postoperative course was normal except for slight wound infection. The patient was discharged on the seventeenth postoperative day (forty-second day postpartum).

The uterus (Fig. 1) measured 15 by 16 by 5 cm. The posterior wall presented a pear-shaped hemorrhagic mass distending the cavity. On microscopic

section through the polypoidal mass, layers of blood and fibrin covered and enmeshed numerous chorionic villi. Centrally, they were more crowded and often viable. At the periphery shadow forms and others in varying phases of necrosis were noted. The underlying layer of decidua compacta was well preserved, and a zone of fibrinoid material separated the placenta from the uterine wall. The underlying veins and arteries were thick and hyalinized. Recanalization of the arteries was present. The veins were hyalinized and filled with thrombi.

### Diagnosis

The diagnosis of retained placental fragments is easily established by the history of recurrent episodes of bleeding within the postpartum period. Hemorrhage resulting from separated thrombi at the placental site is rare. Digital exploration reveals multiple polypi which separate with great difficulty. Microscopic examination shows the absence of chorionic villi. A submucous fibroid, traumatized by labor, may produce bleeding during sloughing and detachment of its pedicle. The patulous cervix, however, permits palpation of the uterine cavity, and so the detection of the contained tumor. Inversion of the uterus is easily established by failure to palpate the organ abdominally, while vaginally the protruding fundus is noted through the tight cervical ring.

### Therapy

In older literature, medical therapy was strongly endorsed for l.p.p.h., in the hope of attaining spontaneous expulsion of the retained fragment. The risk of infection, and the possibility of operative perforation of the uterus largely dictated this course. DeLee thus advocated temporization until the fifth to sixth week postpartum, then, if intervention were still necessary, removal of the fragment by use of the placental forceps. Williams<sup>13</sup> advised digital palpation of the uterine cavity, localization of the retained fragment, and removal by curette. Siegel<sup>9</sup> advocated curette during the first eight days postpartum, and interdicted against the uterine pack because of the danger of infection. He objected to the use of the curette in the early postpartum period, because of the possibility of uterine perforation, and because of secondary hemorrhage from detachment of thrombi at the placental site. After the twelfth to fourteenth day, he advised curette, followed by the use of the dull broad curette, if the latter were necessary. N. H. Williams,<sup>12</sup> however, deplored "obstetrical treatment" (curette, curettage, and uterine packing), and stated that it is productive of the highest mortality. In the five cases comprising his series of l.p.p.h., it was only beneficial in one case, and useless or harmful in all the others. Williams leans to radical removal of the uterus as treatment of l.p.p.h.

In retrospect, we have followed a middle course. The medical and surgical measures employed are shown in Table III. In general, medical therapy proved unsatisfactory. It consisted in the administration of a course of  $\frac{1}{2}$  grain of ergotrate tablets every four hours for six doses, or  $\frac{1}{2}$  e.e. of pituitrin every hour for four doses, associated with bed rest. Employed in 12 cases of the afebrile group, it was without result, for the bleeding, though temporarily lessened, soon recurred. It is noted as successful, however, in Case 2 of the

spontaneous group. In the febrile group medical therapy was similarly unsuccessful in five of seven cases in which it was employed. Surgical intervention was, therefore, ultimately necessary in all cases. This included curettage, curage, and use of the placental forceps. In the afebrile group, two were treated by curage and 16 by curettage. An additional patient was packed after curettage, and in five others curettage followed the attempted removal of the fragment by curage and ovum forceps. In the febrile group four patients were treated by curettage, two by curettage and uterine pack, and one by curage, ovum forceps, and curettage. Transfusion was used in 11 of the afebrile group, either pre- or postoperatively or both, using glucose and saline, or plasma intravenously until the arrival of blood. In the febrile group five of seven patients received blood. In the polyp group one was treated by curettage, and the remaining case ultimately required hysterectomy.

### Morbidity

In the afebrile group of 24 cases, 18 had a normal postoperative course, while six were febrile (Table III). The longest morbidity was four days. The shortest morbidity of one day was associated with a temperature of 100.6° F. In the preoperative "febrile group" of seven cases, two were afebrile following emptying of the uterus, and five continued with temperature. The morbidity, however, was not severe. Three cases had a morbidity of one, two, and three days, respectively. A fourth case ran a temperature of six days, and the fifth patient a febrile course for seventeen days. This last instance was due to thrombophlebitis. In both febrile and afebrile groups there was no incidence of parametritis, peritonitis, or uterine perforation. The prophylactic use of sulfonamides and penicillin is indicated as a pre- and postoperative measure, and is imperative in the febrile group. Routine employment of uterine cultures at the time of curettage would be helpful in the choice and dosage of these drugs.

### Uterine Factors in Late Postpartum Hemorrhage

In the absence of placental fragments, l.p.p.h. is rare. Two uterine factors present as causes: (1) late detachment of thrombi at the placental site with reopening of vascular sinuses and bleeding; and (2) abnormalities in the retention and separation of the decidua vera.

(1) Late detachment of thrombi from the placental site (also designated as "Noninvolution of the Placental Site," by Rutherford and Hertig<sup>6</sup>) was reported by Kustner<sup>7</sup> in 1910. In his two cases liberation of vascular thrombi from the placental site caused profuse bleeding. To understand this factor in l.p.p.h., it may be well to summarize the anatomicophysiological status of the postpartum uterus, as described by Goodall in 1909. In the arteries the fibrous tissue of the media and adventitia undergo hyaline degeneration, and the elastica interna becomes swollen and degenerated. The hyaline of the muscle coat then invades the elastica interna, and enters the vessel lumen replacing the blood clot, so that the lumen is ultimately occluded by hyaline substance, and the artery thus is obliterated. When hyaline thrombosis in the arteries has been partial or absent, the hyaline becomes invested with en-

endothelial cells which form the lining of a new vessel. Next to this new lumen, the hyaline material is invaded by spindle and fusiform cells which later differentiate into muscle cells and fibroblasts, and a new vessel is thus formed within the old, only remnants of the elastica interna and media of the old vessel normally persisting at the periphery (Fig. 2). In postpartum vascular subinvolution, abnormally large amounts of elastic tissue persist about the newly formed artery. In the veins which have no definite elastica interna, all walls contain elastic fibers intermingled with fibrous tissue. In the postpartum period the fibrous tissue swells and becomes hyalinized, thus reducing the lumen of the vein which is filled with clot (Fig. 3). In normal involution, the hyaline in the vein wall is later reconverted into elastic tissue. No detailed description is given of the venous clot. J. Whitridge Williams<sup>10</sup> in 1931 showed that the occluded vessels of the placental site are ultimately undermined by the proliferation of adjoining endometrium, and are lifted from the uterine wall. Protruding as a polypoidal mass, the vessels of the placental site are completely extruded from the organ about the seventh week postpartum.

More recently, Rutherford and Hertig<sup>8</sup> reported three cases of l.p.p.h. due to defective thrombosis in the vessels of the placental site. The first patient, curetted six weeks postpartum, showed only partially obliterated vessels. The second, curetted on the fifteenth day postpartum, showed numerous patent blood vessels at the placental site. Hysterectomy in the third case performed on the twenty-ninth day showed a hemorrhagic polypoidal mass projecting into the uterine cavity. Retained villi were present. Though the arteries were obliterated, many vessels (nature not stated) were incompletely obliterated, for erythrocytes were lying free in their lumina. Two cases of incomplete involution of the placental site were encountered in this study. The clinical features and pathologic reports are as follows:

CASE 1.—(No. 1718) Mrs. X. R., aged 43 years, a gravida viii, para vii, was delivered prematurely of twins at twenty-eight weeks. Manual removal of the placenta was necessary to control active bleeding. The first five days postpartum were febrile, the highest temperature reaching 101.6° F. on the third day. On the ninth day moderate bleeding occurred which was only temporarily controlled by a course of ergotrate, ice bag, and bed rest. Later that day two additional episodes of frank bleeding occurred, and curettage was accordingly performed. The cervix was found patulous, and the fundus was located 3 fingerbreadths above the symphysis. The curettings consisted of a moderate amount of hemorrhagic material. The postoperative course was febrile, the highest temperature reaching 102.4° F. on the fifth postoperative day. There was recurrence of bleeding on that day sufficiently severe to require packing of the uterus and vagina, and the administration of a transfusion of 1,750 c.c. of whole blood. Thereafter, the postoperative course was afebrile, and the patient was discharged on the thirtieth postpartum day when her anemic picture cleared.

The specimen grossly consisted of several irregular hemorrhagic fragments. Placental tissue was not grossly recognizable. Microscopically, the largest fragment was covered with degenerated decidua. The decidual cells had been reduced to hyaline shadow masses. Occasional ones retained their degenerated pyknotic or karyolytic nuclei. There was intensive exudation of lymphocytes and plasma cells which extended into the underlying muscular coat. The superficial muscle fasciculi encircled four contiguous veins (Fig. 4). The endothelial cells were not sharply defined, but occasional swollen and degenerated forms could be distinguished. The muscle and adventitial coats showed swelling and hyalinization. The lumina were filled with feebly formed



Fig. 2.

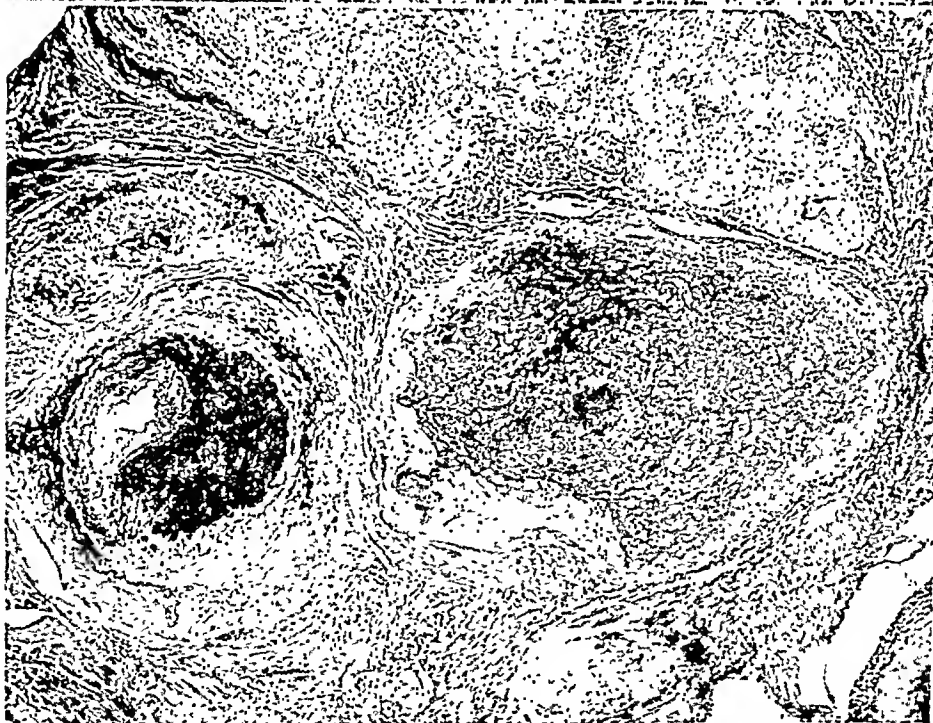
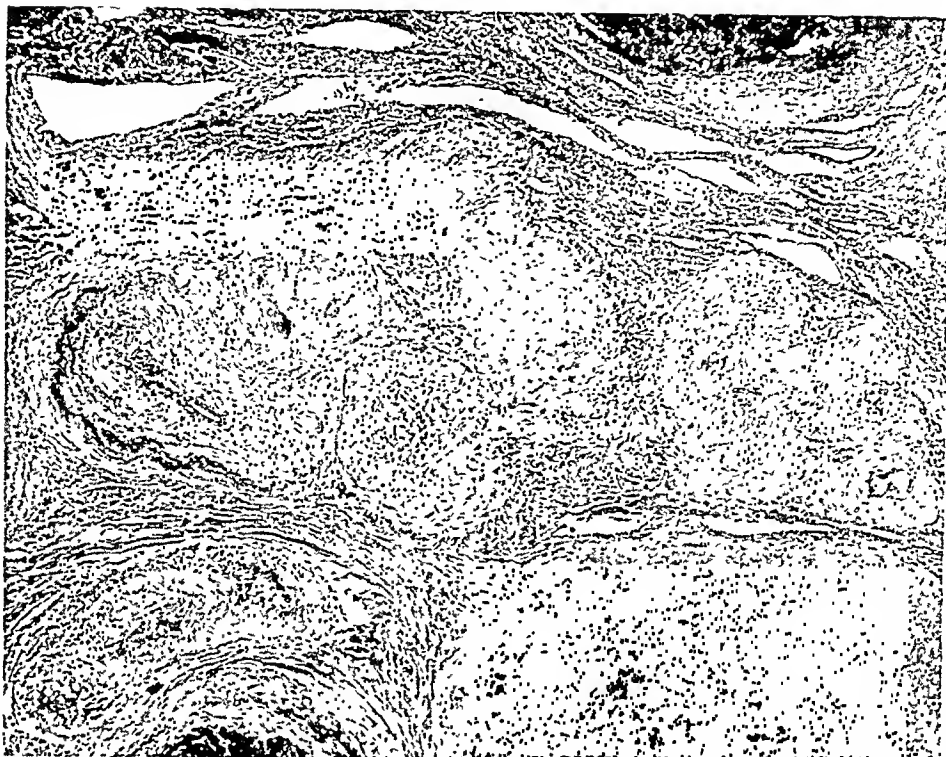


Fig. 3.

Fig. 2.—( $\times 40$ ) Placental site in a uterus removed by hysterectomy for fibroids ten days postpartum. Centrally, the vessels are of arterial type. Many have been completely obliterated. Others are recanalized. The spindle cells about the lumen will form the new media and adventitia. The wavy grey-white tissue at the periphery is the degenerated elastica interna of the old vessel.

Fig. 3.—( $\times 80$ ) The large vessel to the right is a thrombosed vein at the placental site. Note the meshes of fibrin arranged in dense bands or delicate fibers. To the left lies a partially closed artery. The internal elastic membranes of the old vessel is still recognizable. The central clot is poorly formed. Recanalization has begun.

clots (Fig. 4). Only occasionally was fibrin discernible, but platelets were not identified. Surrounding the large venous sinusoids were involuting arteries. More deeply in the section there were smaller veins which showed blood clot invaded by endothelial and fibroblastic cells. Fibrin was abundant. The remaining fragments of tissue were comprised of amorphous necrotic debris infiltrated with polymorphonuclear leucocytes. Occasional areas of regenerating endometrium were encountered.



Fig. 4.—(X80) Veins of the placental site. The distended vessels are filled with blood clot. Thrombosis is poor. Platelets and fibrin are lacking. The red cells are free.

CASE 2.—(No. AA166-528) a gravida iii, para iii, aged 35 years, delivered spontaneously after a labor of eight hours. After thirty minutes in the third stage, manual removal of the placenta was performed because of persistent bleeding. The puerperium was uneventful until the sixth postpartum day, when moderate bleeding appeared. This was seemingly controlled by a course of ergotrate. On the nineteenth postpartum day, however, profuse bleeding recurred. The cervix was found patulous, and the uterus was felt 4 finger-breadths above the symphysis. Curettage yielded several fragments of hemorrhagic tissue. The postoperative course was uneventful, and the patient was discharged on the fifth postoperative day. The pathologic report follows:

Several of the endometrial fragments were completely relined, the lining cells varying from low to medium columnar. The underlying stroma, however, was obscured by dense collections of lymphocytes and plasma cells. The component stromal cells were spindle, round, or fusiform. Other fragments, however, presented degenerating and hyalinized decidua at the surface, while the glands which lay subjacent were large and irregular. Their lining cells were low columnar, and the nuclei presented varying tints. The largest fragments were evidently derived from the placental site. The surface tissues overlying the muscle showed advanced necrosis, and in areas even the muscle cells were necrotic. Several veins lying near the surface presented degenerating hyaline walls (Fig. 5). A well-formed layered clot of red cells and platelets was present in the largest vein, but no fibroblastic invasion was seen

nineteen days after delivery. The smaller veins were surprisingly free from fibrin network, and the red cells appeared free.

It is apparent that in Case 1 clotting was initially poor. In Case 2 organization of the venous thrombi was delayed. Additional studies of normal postpartum uteri appear indicated for complete facts of normal thrombosis at the placental site.



Fig. 5.—( $\times 40$ ) Fragments from the placental site obtained by curettage. A large vein is surrounded by fasciculi of uterine muscle. The concentric layering of the clot is well shown. Thrombosis is adequate. The pale areas correspond to layers of platelets. Organization of the clot, however, is lacking on the nineteenth day following delivery.

(2) Recognition of abnormalities of decidual retention and separation as a factor in l.p.p.h. is due to the work of J. W. Williams.<sup>11</sup> In 50 uteri removed by cesarean hysterectomy, he demonstrated that separation of the placenta and membranes generally occurs in the spongy layer of decidua. The line of cleavage, however, was irregular, so that in some areas thick zones of decidua were retained. This confirmed a similar observation made by Kronig (quoted by Williams in 1901). A later study in 1931 on the postpartum uterus showed that necrosis of any retained decidua is complete by the seventh postpartum day, and that the subsequent detachment of the decidual slough is completed by the twelfth day. At this time the raw surface of the uterus is relined by cells proceeding from the fundi of the uterine glands. By the twenty-first day postpartum, the uterine endometrium has been completely regenerated, except at the placental site. Surprisingly, too, neither decidual nor endometrium infection nor the retention of fetal tissue interfered with regeneration, except at the placental site.

On this anatomic basis, l.p.p.h. can be ascribed to: (a) prolonged retention of normal amounts of decidua; (b) initial retention of excessive amounts of decidua. O. Fränkl<sup>2</sup> indicated that islands of decidua compacta retained in the uterus can proliferate. They become highly vascularized and bleeding proceeds from the "varicose vein plexus" opened during late separation of such decidual islands. Fränkl observed this lesion in six of 23 cases of late bleeding in which there was no other pathology. Küstner, who coined the term "deciduoma," confirmed this observation. Olshausen, Bumin, and others<sup>12</sup> presented similar findings (article by Normal H. Williams).<sup>12</sup> Our series, however, shows no instances of deciduoma, but there were three cases in which decidua was present beyond the twelfth day of the puerperium, a time when all decidua should have been normally detached and expelled. The remaining cases of late postpartum hemorrhage due to this factor must then be explained by the initial retention of abnormally large amounts of decidua. Separation of the membranes occurred at the surface and not through the spongy layer. Whether retained fragments of membrane are contributory, cannot be stated with certainty.

Our attention to the retention of excessive amounts of decidua as a cause of l.p.p.h. was focused by Cases 3, 4, and 5 in which large masses of decidual tissue were spontaneously expelled after an episode of bleeding (Table IV). In two other cases (1 and 2), sizable decidual masses were found in the cervix prior to curettage. All were clinically considered as cases of retained placental fragments until microscopic examination revealed their true character. When the remaining cases of l.p.p.h. without retained placental fragments were reviewed, it was significantly noted that in six of these patients bleeding occurred within the first ten days postpartum (during the time interval for spontaneous slough separation). The early onset of the bleeding and its relative mildness are significant clinical indications of the decidual factor.

TABLE IV. DECIDUAL GROUP

CASE NUM- BER	SYMPTOMS			FEBRILE COURSE			THERAPY		
	ONSET OF BLEEDING IN DAYS	RE- PEATED EPI- SODES	FOUL LOCHIA	PRE- OPERA- TIVE	HIGHEST TEMPER- ATURE	POST- OPER- ATIVE	MEDI- CAL	SPON- TANE- OUS EXPUL- SION	CURET- TAGE
1	Mod.-4th	0	0	1-3rd	101° F. 2nd	0	0	4th	4th
2	Mod.-7th	0	0	0	0	0	7th	7th	7th
3	Mod.-3rd	0	0	0	0	0	3rd	3rd	0
4	Mild-3rd	0	Yes	3-6th	101° F. 3rd	0	3rd	3rd	0
5	Mild-4th	0	Yes	2-5th	101.6° F. 2nd	0	4th	4th	0
6	Mod.-7th	1	0	0	0	0	0	0	9th
7	Mod.-13th	2	0	0	0	0	0	0	15th
8	Mod.-7th	0	0	0	0	0	0	0	9th
9	Mod.-8th	0	0	0	0	0	0	0	9th
10	Mod.-8th	0	0	0	0	0	8th	0	13th
11	Mod.-9th	0	0	0	0	0	9th	0	12th
12	Mod.-11th	0	0	0	0	0	11th	0	11th
13	Mod.-6th	0	0	0	0	0	0	0	6th

Grossly, the material recovered in these cases was noted as moderate but hemorrhagic. The large clotted vessels were prominent. Microscopically, as first described by Williams, the early decidua was infiltrated with blood, and the component decidual cells were necrotic or hyalinized (Fig. 6). In later stages the decidua was reduced to amorphous hemorrhagic debris infiltrated with neutrophils. Only the recognizable hyaline shadow of occasional decidual cells allowed proper morphologic identity (Fig. 7). The vessels of sinusoidal type contained clot almost solely comprised of red cells. Platelets



Fig. 6.—(X80) An elongated sinusoid filled with a poorly formed clot is surrounded by broad sheets of degenerating decidual cells. The latter are spindle or fusiform.



Fig. 7.—(X80) Segment of necrotic decidua. A large empty sinusoid is prominent. Immediately to the right is a zone of necrotic and hyalinized decidua. Isolated degenerating decidual cells are recognizable. In the right lower angle a poorly thrombosed sinusoid is seen.

In addition to other dangers of fetal anoxia, aspiration of amniotic sac contents should receive due consideration. It occurs with great ease, since it requires only about half the effort necessary for aeration. The importance of prevention of anoxia at or near term has been demonstrated by those who studied the effects of the nervous system,<sup>15, 27, 30, 31</sup> and this must be strongly supported from the standpoint of lung pathology.

### Summary

The stages in the fetal or neonatal expansion of the lung are described. If fluid is aspirated, all alveoli expand gradually and simultaneously. If air enters the lung, expansion proceeds by an increase in the number of aerated alveoli; each alveolus either remains collapsed or is fully expanded.

True atelectasis of all or part of the lung tissue is much more common in liveborn than in stillborn infants. This suggests that atelectasis is the normal condition of the fetal lung, and that expansion of the alveoli with fluid as seen in stillborns is the result of an episode of anoxia.

In order to determine the resistance of the lung tissue to expansion, the minimum pressure has been determined which is necessary to fill the alveoli with watery fluid or with air. In the lungs of 15 stillborn or newborn infants thus examined, the average pressure for air is twice that required for fluid. The greater ease with which fluid can be aspirated emphasizes the danger of fetal anoxia and the necessity of its prevention.

The resistance to aeration is due to surface tension which counteracts the entrance of air, but has no effect on the aspiration of fluid. Surface active substances reduce the pressure necessary for aeration. This suggests that the addition of surface active substances to the air or oxygen which is being spontaneously breathed in or introduced by a respirator might aid in relieving the initial atelectasis of newborn infants.

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usually not be distinguished by gross examination at autopsy. Many workers have classified all nonaerated lungs as atelectatic, without considering the possibility of aspiration of fluid. At microscopic examination these two conditions are easily differentiated, but, on the other hand, it is sometimes necessary to pay special attention to the distinction of alveoli expanded with fluid or with air. Only with these points in mind can the findings in the lungs of newborn infants be properly evaluated.

It is obvious that the amount of amniotic fluid present in the alveoli just after birth varies greatly. In general, liveborn infants show less aspirated fluid than do stillborn infants. Table I shows that true atelectasis is much more common in the former group (18 of 30 cases) than in the latter (2 of 30 cases). This suggests that atelectasis is the normal condition of the lungs before birth, as has also been found by some of the above mentioned workers in animal experiments. However, it was mentioned in the introduction that there is no clear-cut and compelling evidence to show whether or not the normal fetus and newborn infant has atelectatic lungs. It is conceivable, and compatible with the present observations in human autopsy material, that the fetus normally aspirates fluid which is then rapidly resorbed at birth so that atelectasis is secondarily established. Against this stands the observation of Farber and Wilson<sup>28</sup> which indicates that in initial atelectasis of the newborn the alveoli have a cuboidal lining which changes irreversibly into a flat lining when the alveoli expand for the first time. Moreover, one would expect to find much more vernix in the lungs of normal newborns than is actually the case if amniotic fluid had regularly been aspirated for a period of several months.

While no final decision is possible at this time, it is felt that the available evidence points more strongly toward the assumption of true atelectasis as the normal condition in the lungs of the fetus at birth. Yet, the presence of aspirated amniotic fluid at autopsy should not indiscriminately be considered as the cause of death. It may be fatal if the amount of fluid or its contamination with solid and fatty material is excessive. A summary of our own interpretation of the various stages in the expansion of the lungs with fluid and air is given in Fig. 1.

The aeration of lung tissue is resisted by surface tension which applies equally to atelectatic alveoli (adhesion of moist surfaces, Wilson and Farber<sup>16</sup>) and to air spaces which contain some fluid but are able to expand further. This resistance does not apply to the entrance of fluid, and that explains why fluid is aspirated so easily and extensively. One may wonder why episodes of anoxia which should occur occasionally during fetal life do not lead to severe aspiration in almost every case. The explanation is given by the fact that near the end of pregnancy the reserve of oxygen available for the fetus and with it the protection against anoxia increases rapidly. The oxygen saturation of the maternal blood returning from the placenta decreases very much during the latter part of pregnancy.<sup>29</sup> The same degree of anoxia of the mother which has a great effect on the fetus near term may not be harmful early in pregnancy because of the small consumption and greater reserve of oxygen.

## ANALYSIS OF THERAPEUTIC ABORTIONS, BELLEVUE HOSPITAL 1935-1945

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THE occasional necessity for the interruption of a pregnancy, to preserve the life of a mother, has been recognized since ancient times,<sup>1</sup> and the difficulty of defining the borderline between such therapeutic procedures and criminal abortions has always existed. Neither the legal nor the medical professions have helped to clarify the issue,<sup>2</sup> since the former has failed to provide a clear statement of society's attitude, while the medical profession has failed to define the conditions which obligate a therapeutic abortion.

In our country, up to the present, each State has established its own legal policy, with a resultant body of law which is inadequate and often conflicting. The legal permission to execute a therapeutic abortion in New York State is contained in the legal code,<sup>3</sup> but this does not describe the conditions to be met.

In 1934, at a symposium held before the Obstetrical, Gynecological, and General Surgical sections of the American Medical Association, the medical complications indicating therapeutic abortion were presented by several leading authorities.<sup>4-8</sup> The suggested principles, which adequately expressed the modern viewpoint, were not accepted by other leading authorities at that time, nor has a greater unanimity been found in the recent literature. Analyses of therapeutic abortions from institutions in different sections of our country,<sup>9-11</sup> have shown a surprising agreement on most indications on the ratio of incidence to the number delivered and on the manner of interruption. Before the New York Obstetrical Society in 1944 a consideration of therapeutic abortion was given by S. A. Cosgrove,<sup>12</sup> which showed a distinct departure in the management of this problem.

### Purpose and Scope

An analysis of the therapeutic abortions performed at Bellevue Hospital from June 1, 1935, to May 31, 1945, was undertaken in order to re-evaluate the policy for this institution. It was found that 199 pregnancies were interrupted on the gynecologic service; while, during the same period, 15,119 were delivered on the obstetric service. The incidence of therapeutic abortion was therefore 1.23 per cent, or this may be expressed as a ratio of one therapeutic abortion to every 76 women delivered.

The age, color, and marital status for the group are presented in Table I. There was no significant variation from the obstetric patients.

### Source of Cases for Therapeutic Abortion

The source of admission was established in each case to determine the initiating request for interruption. From Table II, it can be seen that the department was responsible for 36 per cent of the cases, the several medical



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services within the hospital for 48.4 per cent, and combined opinion for the remaining 15.6 per cent. The tuberculosis service accounted for most of the transfers within the hospital; more cardiac cases arose from the Out-Patient Department than were referred from within the hospital.

### Therapeutic Abortions Refused

The final decision for termination was reached by the gynecologic service at all times, and the prerogative of refusal was exercised at least twenty times during the period covered by this report. These refusals are classified according to proposed indication in Table III. The reasons for refusal were about equally divided between insufficient medical evidence and a duration of pregnancy so late as to indicate equal risk to the mother for delivery at term, or for therapeutic abortion at that time.

### Duration of Pregnancy and Parity

The duration of pregnancy and parity of the women in our series are presented in Table IV.

TABLE IV. DURATION OF PREGNANCY AND PARITY

DURATION OF PREGNANCY IN WEEKS	INCIDENCE	PARITY	INCIDENCE
0-4	1.5	None	26.8
5-8	40.0	I	21.4
9-12	43.0	II	21.4
13-16	14.0	III	8.6
17-20	1.0	IV	10.7
21-24	0.5	V	5.9
		VI	2.1
	100.0	VII	2.1
		VIII	0.5
		IX	0.5
			100.0

### Therapeutic Abortions in Those Patients With No Living Children

It was found that 28.3 per cent of the women in this series had no living children. The therapeutic abortions performed on this group are presented in Table V. The indications vary from the entire group in that tuberculosis is greater by almost 16 per cent, in that cardiac disease and the toxemias of pregnancy were each less by 5 per cent, and the "other" indications were less by 6 per cent. The manner of termination varied in that the sterilizations were less frequent by 20 per cent than in the entire series, and in that there was a greater frequency of the dilatation and curettage operation. It is of interest to note the sterilizations among patients with neurologic and psychiatric complications occurred with slightly greater frequency in these women with no living children than in the group as a whole (71 to 63 per cent).

### Indications for Therapeutic Abortion

The indications for therapeutic abortion have been under constant revision since this procedure was first introduced. The earliest indication<sup>4</sup> noted in the literature of the eighteenth century was for contracted pelvis. In the middle of the next century, a gradually increasing scope was evolved which embraced indications for cardiac disease, tuberculosis, and many neurologic and psychiatric disorders. The use of therapeutic abortion continued to broaden until the

TABLE I. VITAL STATISTICS

AGE		COLOR		MARITAL STATUS	
YEARS	INCIDENCE		INCIDENCE		INCIDENCE
15 and under	1.0	White	94.0	Married	78.3
16 to 20	5.7	Negro	5.0	Single	13.0
21 to 30	63.6	Others	1.0	Divorced	1.0
31 to 40	25.1			Separated	5.7
Over 40	4.6			Widowed	2.0

TABLE II. SOURCE OF ADMISSION

SOURCE OF ADMISSION	INCIDENCE (PER CENT)	OTHER SERVICE INVOLVED	INCIDENCE (PER CENT)
Direct	36.0	None	
By transfer (within hospital)	48.4		
		Tb	37.7
		Medicine	3.8
		Chest	1.1
		Cardiac	3.2
		Neur. & psych.	1.6
		Obstetrics	0.5
		Genito-urinary	0.5
			48.4
Combined (by consult in O.P.D.)	15.6	Cardiac	4.9
		Tb	3.8
		Neur. & psych.	3.8
		Obstetrics	1.6
		Orthopedic	0.5
		Diabetic	0.5
		Radiation therapy	0.5
			15.6

TABLE III. THERAPEUTIC ABORTIONS REFUSED

INDICATION	INCIDENCE	PROCEDURE NECESSARY		DELIVERED ON OBSTETRIC SERVICE
		CURETTAGE	HYSTEROTOMY	INCIDENCE
Tuberculosis				
Minimal	20.0	10.0	10.0	5.0
Moderately advanced	15.0	—	15.0	—
Far advanced	5.0	—	5.0	5.0
Cardiac				
Class I	5.0	—	5.0	—
Class II	15.0	10.0	5.0	5.0
Class III	5.0	5.0	—	5.0
Epilepsy	10.0	—	10.0	5.0
Hypertension and previous history of toxemia	5.0	—	5.0	—
Asthma	5.0	5.0	—	—
Hyperthyroid	10.0	—	10.0	5.0
Thromboecytic purpura	5.0	5.0	—	—
	100.0	35.0	65.0	30.0

10% P.P.  
Sterilizations

and cardiac indications. (5) Bellevue Hospital's report is intermediate in frequency of occurrence, and shows many more interruptions for tuberculosis and many less for the toxemias of pregnancy than any of the other reports.

The individual analyses of the five major groups of indications at Bellevue follow.

1. *Tuberculosis*.—A most vehement controversy centers over tuberculosis as an indication for therapeutic abortion. There is no statement that can be made about this complication but that a diametrically opposite opinion can be quoted from an equally competent source. The high incidence at this hospital results from the large number of tuberculous hospital patients, and from the low socio-economic group we serve. As long as rest remains the essential of treatment, it is impossible for us to expect these people to support the ideal program of reduced activity that is necessary.

The tuberculous indications for interruptions are given in Table VII, showing the percentage occurrence of the pulmonary types, the average duration (in years and months) for each, the manner of terminations, and a five-year trend for all types. The occurrence in the earlier and later five-year periods show that tuberculosis accounts for 41.5 per cent of the total indications in the 1935 to 1940 period, while in the later span it rises to 56.8 per cent. This is partially explained on the regularity with which approximately 9.5 patients are aborted for tuberculosis each year. A different analysis is presented later showing the management of all phases of tuberculosis as far as it concerns the pregnant woman.

TABLE VII. TUBERCULOSIS

	MINIMAL	MOD. ADVANCED	FAR ADVANCED	UNCLASSIFIED
10 year incidence	15.8	56.9	16.8	10.5
1935 to 1940	10.6	25.9	8.4	5.25
Incidence				
1940 to 1945	5.2	31.0	8.4	5.25
Average duration	3 yr. 8 mo.	4 yr. 4 mo.	2 yr. 9 mo.	—
Termination—Type				
Dilatation and curettage	53.3	51.8	62.5	80.0
Hysterotomy	20.0	16.7	12.5	—
Hysterotomy and sterilization	26.7	31.5	25.0	20.0
	100.0	100.0	100.0	100.0

*Incidence of Tuberculosis Indication*

Entire series	47.8
1935-1940	41.5
1940-1945	56.8

2. *Cardiac Disease*.—The greatest unanimity of opinion has been evolved in the cardiac indications for therapeutic abortion. The functional classification is the first essential (the New York Heart Association has been used throughout), and the revelation of any history of failure is ominous. Any Class III cardiac showing decompensation, which does not respond to therapy, is to be considered for interruption. In Class IV cardiacs showing decompensation, the strictest attention toward therapy of the medical status is necessary before any procedure can be adopted. Patients with auricular fibrillation and with certain congenital cardiac malformations are considered a greater risk than others in the same functional class. These indications closely follow those previously reported by Pardee.<sup>5</sup>

The cardiac conditions which indicated therapeutic abortion are presented in Table VIII and are summarized as follows: (1) There were no interrup-

TABLE V. THERAPEUTIC ABORTIONS IN THOSE PATIENTS WITH NO LIVING CHILDREN

INDICATION	INCIDENCE		TYPE OF TERMINATION	INCIDENCE
Tuberculosis	62.3		Dilatation and curettage	72.2
Minimal		11.3	Hysterotomy—abdominal	17.0
Moderately advanced		35.9	Hysterotomy—vaginal	1.9
Far advanced		15.1	Hysterotomy and sterilization	18.9
				100.0
Cardiac	11.3			
Class II		3.8		
Class III		5.6		
Class IV		1.9		
Toxemias	5.7			
Neurological and Psychiatric	13.2		STERILIZATIONS	INCIDENCE
Psychosis		1.9	Tuberculosis	40.0
Epilepsy		7.5	Toxemia	10.0
Multiple sclerosis		3.8	Neurological and psychological	50.0
				100.0
Others	7.5			
Arthritis		1.825		
Carcinoma right breast		1.825		
Diabetes		1.825		
Round-cell sarcoma		1.825		
	100.0	100.0		

turn of this century when the first evidence of conservatism became apparent and the medical profession took a more critical view of the indications.

A comparative analysis of the indications for therapeutic abortion from several leading hospitals is given in Table VI. From this, several points are noteworthy: (1) The period covered by the Johns Hopkins report, being much earlier than the others, shows the greatest frequency of interruptions. (2) The incidence at the Chicago Lying-in Hospital is the lowest of the standard type reported and shows greater emphasis on the toxemia indications. (3) The whole number and ratio of incidence for the Margaret Hague Maternity Center are not a matter of having fewer therapeutic abortions than any of the other services, but of being in an entirely different class. (4) The significant differences in New York Lying-in Hospital's report is in the incidence of toxemia

TABLE VI. COMPARISON OF INSTITUTIONS

THERAPEUTIC ABORTIONS	BELLEVUE	JOHNS HOPKINS <sup>9</sup>	CHICAGO LYING-IN <sup>10</sup>	MARGARET HAGUE <sup>12</sup>	NEW YORK LYING-IN <sup>11</sup>
Number reported	199	287	134	4	280
Years covered	1935-1945	1896-1934	1931-1939	1931-1943	1932-1943
Ratio to number delivered	1:76	1:35	1:195	1:16750	1:167
Indications					
Tuberculosis	47	10	24	—	11
Cardiac	16	13	20	—	24
Neurological and psychological	13	17	15	—	6
Toxemias	10	46	28	100	35
Others	14	14	13	—	24
	100	100	100	100	100

cates interruption. The indications presented in Table IX show a pronounced diversity, but the repeated occurrence of the first four diseases in other reports<sup>8-10</sup> indicates some uniformity of thought on certain disorders. The outstanding features in this group of therapeutic abortions are shown in the high incidence of sterilizations and in the markedly decreasing incidence of occurrence.

4. *Toxemias of Pregnancy and Pyelitis.*—The toxemias of pregnancy are in themselves on the decline in most parts of the United States because of the increased availability of antepartum care and the early treatment of the first signs of the disorder. Naturally, a fall in the incidence of therapeutic abortions for this indication has followed. Pyelitis of pregnancy has been placed with this group, since we felt that it more closely aligns itself to the toxemias of pregnancy than to any other group.

The analysis of the factors favoring interruption for the toxemias and for pyelitis (Table X) is only of limited significance, since many of these patients evidenced two or more factors at the time the therapeutic abortion was per-

TABLE X. TOXEMIAS OF PREGNANCY AND PYELITIS

TYPE	INCIDENCE	DILATATION AND CURETTAGE	HYSTEROTOMY	HYSTEROTOMY AND STERILIZATION
Hypertension	15.	66.6	—	33.3
Hyperemesis gravidarum	5.	100.0	—	—
Pre-eclampsia	5.	—	—	—
Previous history of toxemia	55.	54.5	9.1	36.4
Pyelitis	20.	75.0	—	25.0

*Incidence of Toxemia and Pyelitis Indication*

Entire series	10.1
1935-1940	9.3
1940-1945	11.1

TABLE XI. "OTHERS"

INDICATIONS	1935-1940 INCIDENCE	1940-1945 INCIDENCE	TOTAL	DILATATION AND CURETTAGE	HYSTER- OTOMY	STERILIZA- TION AND HYSTER- OTOMY
Diabetes	14.9	3.7	18.6	80	—	20
Ulcer	11.1	3.7	14.8	75	—	25
Neoplasms	14.8	—	14.8	100	—	—
Asthma	11.1	—	11.1	66.6	—	33.3
Bronchiectasis	3.7	3.7	7.4	50	—	50
Hyperthyroidism	7.4	—	7.4	100	—	—
Tuberculous familial diathesis	3.7	—	3.7	—	100	—
Arthritis	3.7	—	3.7	100	—	—
Congenital polycystic kidney	3.7	—	3.7	Not determined		
Marie-Strumpel's disease	3.7	—	3.7	100	—	—
Malnutrition	3.7	—	3.7	—	100	—
Gall bladder disease	—	3.7	3.7	100	—	—
Hemophiliae heredity	—	3.7	3.7	—	—	100
Total	81.5	18.5	100.0			

*Incidence of "Others" Indication*

Entire series	13.5
1935-1940	18.7
1940-1945	6.2

tions in Class I cardiac disease. (2) Class II cardiac indications were four and one-half times more frequent in the earlier five years covered in this report. (3) Class III cardiac indications comprised almost one-half of this group. (4) Of all these cardiac cases, 15 per cent were in failure during the gestation interrupted. (5) Stander<sup>13</sup> reported a 2.55 per cent interruption incidence among his Class II and Class III pregnant cardiacs, as contrasted to a 0.2 per cent incidence for all pregnant cardiacs at this hospital.

TABLE VIII. CARDIAC

	CLASS I	CLASS II	CLASS III	CLASS IV	UNCLASSIFIED
10 YR. INCIDENCE	—	33.3	48.5	3.0	15.2
1935 to 1940	—	27.2	18.2	—	9.1
Incidence 1940 to 1945	—	6.1	30.3	3.0	6.1
Average duration in years	—	11.75	13.66	14.0	—
Termination—Type					
Dilatation and curettage	—	45.5	37.5	—	—
Hysterotomy	—	18.1	12.5	—	—
Hysterotomy and sterilization	—	36.4	50.0	100.0	100.0
		100.0	100.0	100.0	100.0

*Incidence of Cardiac Indication*

Entire series	16.6
1935-1940	16.1
1940-1945	17.3

3. *Neurology and Psychiatry.*—The trend in the evaluation of these disorders as an indication for therapeutic abortion has swung from comparative liberalism to marked conservatism in the past twenty years. There does not seem to be any one condition in neurology or psychiatry which absolutely indi-

TABLE IX. NEUROLOGY AND PSYCHIATRY

INDICATION	1935-1940 INCIDENCE	1940-1945 INCIDENCE	TOTAL	DILATATION AND CURETTAGE	HYSTER- OTOMY	STERILIZA- TION AND HYSTER- OTOMY
Epilepsy	8.3	12.6	20.9	20	—	80
Parkinson's disease	12.6	8.3	20.9	60	—	40
Multiple sclerosis	8.3	4.2	12.5	—	—	—
Psychoses	12.3	4.2	16.5	25	—	75
Residuals of poliomyelitis	8.3	—	8.3	50	—	50
Brain tumor	4.2	—	4.2	—	—	100
Amaurotic family idiocy	4.2	—	4.2	—	—	100
Chorea and psychoses	4.2	—	4.2	—	—	100
Mental deficiency	4.2	—	4.2	—	—	100
Familial psychosis tendency	4.2	—	4.2	Not determined		
Total	70.9	29.1	100.0			

*Incidence of Neurotic and Psychologic Indications*

Entire series	12.0
1935-1940	14.4
1940-1945	8.6

were not recognized and fibrin was scant or lacking. Reopening of such poorly thrombosed sinuses during separation of the decidual slough with resulting hemorrhage appears well founded.

In the decidual group of 13 cases, the important clinical manifestations are indicated in Table IV. Nine patients were primiparas and four were multiparas. Seven were delivered spontaneously, while six required the use of forceps. The third stage of labor was without complication. In all instances there was spontaneous separation of the placenta followed by modified Créd . As expected from the physiologic considerations presented above, the bleeding as a rule presented within the first ten days, and in only two of the 13 cases did hemorrhage appear after the tenth day. Contrasted with "retained placental group," the bleeding was relatively mild, and shock was not encountered. Pain was not a symptom. The lochia was noted as foul in only two cases. Three patients showed mild preoperative febrile courses. Upon physical examination large shreds of tissue had been spontaneously expelled into the vagina in three patients. In two other instances, the decidua was loose and retained in the cervix. In all instances the cervix was patulous and the uterus was generally designated as subinvolved. Medical therapy was employed in seven cases. Of these, three required no further treatment. In four of the five instances, where complete or partial expulsion of tissue was noted, ergotrate had been used. Ten cases were curetted. As a rule this therapy was instituted between the fourth and the fifteenth days. There were no postoperative reactions, and transfusions were only necessary in one case (No. 13). It is apparent that this group of l.p.p.h. is of mild type, and, if recognized, curettage may be avoided.

### Conclusions

1. Retention of placental fragments is the most frequent cause of late postpartum hemorrhage. The retained fragment may be spontaneously expelled. More commonly, however, recurrent episodes of bleeding require surgical intervention. Formation of placental polypi is infrequent.

2. Digital exploration of the uterus is the only sure method of diagnosis; the other physical findings are insufficient.

3. Treatment of the retained placental fragment is surgical. Separation by the finger (cavage) is the method of choice. If unsuccessful, the use of the curette, or ovum forceps is safe. Such operative intervention for active bleeding in febrile cases is followed by moderate morbidity.

4. Uterine factors as causes of late postpartum hemorrhage have not heretofore been sufficiently emphasized. Noninvolution of the placental site is evidenced by poorly thrombosed veins which reopen and produce late secondary bleeding. The placental site requires restudy in normal postpartum uteri.

5. Retention of abnormal amounts of decidua vera during separation of the placenta and membranes is causative of the milder type of late postpartum hemorrhage.

6. Digital exploration of the uterine cavity is the first step in the treatment of late postpartum hemorrhage. Only by this method can a retained placental fragment be discovered and then removed. If no placental fragment is present, noninvolution of the placental site or separation of excessive amounts of decidual slough are the causative factors of the bleeding.

Thanks are herewith extended to the members of the Obstetrical and Gynecological staffs for permission to include their personal cases in this study.



formed. Any previous history of toxemia, when coupled with any of the others, weighed the evidence heavily toward interference.

5. "*Others.*"—This group includes all of the remaining indications for therapeutic abortion. Each is a problem unto itself and requires the keenest individual evaluation. Several can be removed from the present-day indications for therapeutic abortion by recent advances in medical management. The decreasing incidence of this group of indications is the outstanding feature of Table XI.

### Trends During the Ten-Year Period (1935-1945)

The summary of indications in Table XII presents the 1935-1940, 1940-1945 and the ten-year totals for all indications. A significant trend is noted between the earlier period when 59.3 per cent of the total were aborted—with a ratio of 1 to every 64.4 women delivered—as against only 40.7 per cent of the total for the later period—with a ratio of 1 to every 93 women delivered. This trend generally follows the conservatism which has become manifest in the indications for all therapeutic abortions. The relative trends within groups show an apparent increase in tuberculosis and an apparent unchanged incidence in the cardiac and toxemia-pyelitis indications. Further clarification is shown in a later analysis. The decreases in the other two groups are definite trends which account for the changes in the incidence for the two five-year periods.

TABLE XII. SUMMARY OF INDICATIONS

	1935-1940 TOTAL	1940-1945 TOTAL	10-YEAR TOTAL
Distribution	59.3	40.7	100.0
Indication			
Tuberculosis	41.5	56.8	47.8
Cardiac	16.1	17.3	16.6
Toxemias	9.3	11.1	10.1
Neurological and psychiatric	14.4	8.6	12.0
Others	18.7	6.2	13.5
	100.0	100.0	100.0
Number delivered	7602.0	7517.0	15119.
Therapeutic abortions	118.0	81.0	199.
Ratio	1:64.4	1:92.8	1:75.9

### Note on Fetal Indications for Abortion

Two recent advances in the cause of fetal pathology suggest additional indications for therapeutic abortion. P. Levine<sup>14</sup> has found it advisable to recommend interruption in six very carefully selected cases. The criteria are Rh-negative women already immunized from preceding pregnancies which had resulted in one or more erythroblastic infants with fatal forms of the disease, and whose husbands were such as to exclude the possibility of an Rh-negative infant. In the other instance, Albraugh<sup>15</sup> has shown that a high incidence, and at times 100 per cent of the infants born to mothers who have had rubella in the early months of pregnancy, show severe congenital anomalies. The possibility to interrupt pregnancies for both the above conditions warrants serious consideration.

### Repetition of Abortion in the Same Patient

A review of the past histories of these 199 women revealed that five therapeutic interruptions had been performed at other hospitals prior to their

Bellevue admissions. Among the 199 therapeutic abortions at Bellevue, eight were repeats on the same patients. This gives a gross repeat percentage of 6.5, of which 4 per cent occurred at this hospital. The indications of both therapeutic abortions were identical in each of these patients.

### Technique of Interruption

The type of termination and the anesthesia preference are shown in Table XIII, according to the major groups of indication. The manner of termination was limited to operative procedures, in spite of the reported success of some observers with X-ray. The anesthesia department was consulted before any procedure was undertaken, and their preference followed.

TABLE XIII. MANNER OF TERMINATION

	TUBERCU- LOSIS	CARDIAC	NEUROLOGICAL AND PSYCHI- ATRIC	TOXEMIA	OTHERS
Curettage	57.0	33.3	30.5	60.0	75.1
Hysterotomy	14.7	9.2	—	—	7.7
Hysterectomy	—	3.0	4.3	5.0	3.8
Hysterectomy and sterilization	28.3	54.5	65.2	35.0	15.4
	100.0	100.0	100.0	100.0	100.0
ANESTHESIA PREFERENCE					
Cyclopropane	70.0	40.0	13.4	55.0	45.4
Gas-oxygen-ether	24.0	46.6	73.6	45.0	22.8
Gas-oxygen	—	10.0	8.7	—	22.8
Local	3.6	3.4	4.3	—	4.5
Spinal	1.2	—	—	—	—
Other	1.2	—	—	—	4.5
	100.0	100.0	100.0	100.0	100.0

### Mortality

There was only one death among the entire series. This mortality rate of 0.5 per cent compares favorably with other reported rates. The history of the fatal case illustrates the error that can be made in the treatment of tuberculosis. A 19-year-old white girl was referred by the chest service for interruption, with a bilateral tuberculosis of six months' duration. A previous request for interruption by dilatation and curettage was refused because of the duration of the pregnancy. After considerable debate, in which the tuberculosis service considered interruption imperative to save the life of the girl, the hysterotomy was performed under spinal anesthesia. Death ensued on the sixth postoperative day from an extensive fibrocaseous, tuberculous, pneumonic consolidation of both lungs.

### Therapeutic Abortions Versus Delivery

The ratio of therapeutic abortions to the number delivered has been given, but it is believed that this figure is of little value. A more valuable approach is a study of the number therapeutically aborted as compared to the number of deliveries accomplished in women suffering from the same medical complications. This is presented in Table XIV and affords an opportunity to study the end obstetric result.

TABLE XIV. COMPARISON OF THERAPEUTIC ABORTIONS PERFORMED TO THE NUMBER DELIVERED WITH THE SAME COMPLICATION  
INCIDENCE PER 1,000 DELIVERED

	1935-1940		1940-1945		TOTAL OBSTETRIC	TOTAL THERA- PEUTIC ABORTIONS
	OBSTETRIC	THERA- PEUTIC ABORTION	OBSTETRIC	THERA- PEUTIC ABORTION		
Tuberculosis	10.0	6.5	14.6	6.1	12.3	6.3
Cardiacs	18.8	2.3	28.0	1.9	23.4	2.1
Toxemia						
Unclassified type	30.4		33.5		31.95	0.8
Hyperemesis	2.6		6.1		4.35	0.1
Pre-eclampsia	16.4		28.1		22.25	0.1
Eclampsia	1.5		2.4		1.95	—
Hypertension	21.3		23.9		22.60	0.3
Nephritis	0.9		0.9		0.9	—
	73.1	1.5	94.9	1.1	84.00	1.3

From the ten-year study of women delivered with and aborted for tuberculosis complicating pregnancy, the total incidence of the complication was found to be 18.6 per each 1,000 women delivered. Of these 18.6 women, 12.3 had been carried to term, and 6.3 had been therapeutically aborted. The trend in management, from a study of the 1935-1940 and 1940-1945 periods, revealed the number aborted for tuberculosis to have dropped by 6 per cent (6.5 to 6.1), while the number carried to term had risen by 32 per cent (10.0 to 14.6). This reveals then an increasing conservatism in the indication of tuberculosis for therapeutic abortion when one considers the over-all management to be given the pregnant, tuberculous woman. This study negates the erroneous impression of an increasing incidence of tuberculosis as an indication for therapeutic abortion obtained from a study of indications only.

In a similar study of cardiac disease in pregnancy, the total incidence was 25.5 per 1,000 women delivered, of whom 23.4 were carried to delivery, and of whom 2.1 required interruption. In a study of the management of the pregnant cardiac, the five-year analyses revealed a decrease of 15 per cent in the number aborted for cardiac disease (2.3 to 1.9), while the number carried to delivery rose by 33 per cent (18.8 to 28.0). This again shows a decreasing incidence in the employment of therapeutic abortion as a measure in the management of the pregnant cardiac patient, as against a fixed incidence suggested by a study of indications only.

A like study of the toxemias of pregnancy revealed a total incidence of 85.3 per 1,000 delivered, of whom all but 1.3 can expect to carry to term. The trend study revealed a decided drop of 26 per cent in the number aborted for the toxemias of pregnancy (1.5 to 1.1), coupled with a 23 per cent rise in the number delivered with the same complication (73.1 to 94.9). This again dispels the impression of a fixed occurrence incidence suggested by a study of the indications.

Maternal Mortality

A study of maternal mortality which concerns therapeutic abortion is presented in Table XV. For the 1935-1945 period studied, the total maternal mortality was 2.8/1,000, of which 0.7/1,000, or one-fourth, of these deaths resulted from medical complications for which therapeutic abortions have been performed. This proposes that, despite the current enthusiasm for conservatism, the ideal in management is yet to be reached.

TABLE XV. 10-YEAR MATERNAL DEATH RATE

All causes	2.8 /1000
Tuberculosis (Far advanced)	0.14/1000
Cardiac	0.07/1000
Psychosis	0.07/1000
Toxemias	0.21/1000
Toxemia and psychosis	0.07/1000
Carcinoma	0.14/1000
Total	0.70/1000

### Summary and Conclusions

1. A series of 199 consecutive therapeutic abortions performed at Bellevue Hospital from June 1, 1935, to May 31, 1945, has been reviewed.

2. Tuberculosis was the major indication for therapeutic abortion at this hospital, accounting for 47.8 per cent of the cases.

3. A lesser incidence of interruption for the toxemias of pregnancy (10.1 per cent) was found in this series than has been reported elsewhere.

4. From a comparison of the number of therapeutic abortions performed to the number delivered with the same medical complication, it was found that the indications for all therapeutic abortions are on the decrease, whereas the number delivered with the same medical complication is on the increase.

5. From all evidence in this study, the policy in effect at Bellevue Hospital from 1935 to 1945 has been justified. Its continuation in the future is warranted until additional scientific data justify modification or change.

The author wishes to express his indebtedness to Dr. Howard C. Taylor, Jr., for his invaluable guidance and cooperation in the preparation of this paper.

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20 HILLSIDE AVENUE

## LATE POSTPARTUM BLEEDING: A METHOD OF PREVENTION

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EVERY year at least six patients have been readmitted to the Elizabeth Steel Magee Hospital on account of excessive bleeding, occurring from thirteen to forty-two days following delivery. All have needed dilatation, curettage, and packing of the uterus. Some have required plasma or blood transfusions, and their average hospital stay has been 8.4 days. Besides these actual hospital admissions, there have been countless telephone calls and numerous house visits necessitated by mild to moderate persistent postpartum bleeding. The time, expense, annoyance, and potential hazard involved add up to a considerable problem. Is there some method by which this complication, nuisance, and even potential threat to the patient's life can safely be avoided—thus saving time, money, hospital beds, and annoyance both to the patient and the obstetrician? We feel that if obstetric patients are carefully observed and treated following delivery this complication need not remain unrecognized and uncorrected.

A lochia rubra which persists for more than six or seven days post partum is abnormal and may be dangerous. The principal causes are retained secundines with subinvolution of the uterus and, as demonstrated by Rutherford and Hertig,<sup>1</sup> failure of involution of the placental site itself without retention of placental tissue and possibly without subinvolution. How can we confirm one or the other diagnosis, and what treatment is feasible and safe?

Before answering this, let us review our routine management of the third stage of labor. At the end of the second stage, an ampule of pitocin is given subcutaneously. The episiotomy is then repaired. We do not massage the uterus until placental separation has occurred, unless hemorrhage necessitates interference. When upward pressure on the anterior uterine wall above the symphysis does not cause the cord to be drawn into the vagina the placenta is free. After light massage to make the uterus firm, the placenta is expressed and is closely examined for deficiencies. If none are found an ampule of ergonovine is given subcutaneously or intravenously, following which a course of  $\frac{1}{320}$  grain of ergonovine, three times a day for three days, is ordered. Despite such conservative handling of the third stage of labor, retention of small pieces of placenta cannot be prevented in all cases, because small defects in the placenta cannot always be detected even by careful examination.

If placental tissue is retained, or if there is subinvolution of the placental site, the characteristic clinical signs during the postpartum hospital period are:

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1. Lochia rubra persisting beyond the sixth or seventh day.
2. Subinvolution of the uterus.
3. A persistent low-grade temperature of 99° to 100° F., or even slightly higher in the majority of cases.

As treatment, we have tried a second or even a third course of ergonovine together with a sulfonamide; but uniformly satisfactory results have not been attained. Our subsequent approach is more active than passive. According to the latter school retained placental tissue, unless hemorrhage necessitates interference, should be left alone, in the hope that it will eventually slough out. We employ the following routine: if by the eighth or ninth postpartum day lochia rubra persists, unless the temperature is definitely septic in character, a pelvic examination is made in bed. The labia are widely separated and, using a sterile glove, two fingers are introduced into the vagina, keeping as close as possible to the symphysis so that the episiotomy is not broken down. The uterus is usually found to be anteflexed and the cervix patulous. With the outside hand, the axis of the uterus is straightened, and the second finger is introduced through the open cervix. The fundus is then pushed down so that the examining finger can explore the entire cavity. In practically all cases a piece of tissue or a marked elevation on the uterine wall can be felt. With this confirmation, and unless there is a marked reaction to the pelvic examination, the patient is taken to the operating room the next day. Under anesthesia, a placental forceps is introduced into the uterus, the tissue is grasped and removed with a twisting motion, and the uterine cavity is then packed. Recently we have also been giving penicillin prophylactically for forty-eight hours. Following the removal of the packing in twenty-four hours, the temperature usually drops to normal and the patient is, in most instances, discharged on the fifth postoperative day. If on initial examination no placental tissue is felt, a course of ergonovine usually gives satisfactory results.

Before presenting our statistics, two typical case histories will be given and characteristic temperature charts shown. Mrs. C. M., gravida i, at term, was delivered spontaneously after a labor of a twelve-hour first stage, thirty-five-minute second stage, and twenty-five-minute third stage. The placenta separated by the Schultze mechanism and on inspection was considered intact. The postpartum course was febrile, with the temperature varying between 99° F. and 102.2° F. On the eighth day post partum the fundus was three fingerbreadths above the symphysis, there was persistent lochia rubra, the temperature was 100.4° F., and on vaginal examination a piece of placental tissue was felt in the fundus. A mild febrile reaction following examination deferred operation until the eleventh day, at which time, under sodium pentothal anesthesia, placental forceps were used to remove the retained tissue, and the uterine cavity was packed. Twenty-four hours later the packing was removed, the temperature dropped to normal, and the patient was discharged on the seventeenth postpartum day.

Mrs. K. P., gravida iii, estimated date of confinement July 12, 1940, came into the hospital July 15 in active labor. After an inertial labor of a seventy-three-hour and twenty-minute first stage, a sixteen-minute second stage, and a

nine-minute third stage, she was delivered spontaneously of a living 8¾ pound male infant. The placenta was expelled by the Duncan mechanism, and was considered intact. The temperature varied between 99° F. and 100° F. post partum, and there was persistent lochia rubra. Pelvic examination on the ninth postpartum day revealed a subinvolted uterus with placental tissue on the anterior wall. Dilatation, evacuation, and packing were done on the eleventh day. Twenty-four hours later the packing was removed, the temperature dropped to normal, and four days from the time of operation the patient was discharged.

From Jan. 1, 1938, to Jan. 1, 1946, we performed 134 postpartum evacuations and packings on 85 private and 49 ward patients. All patients were estimated to be of at least seven months' gestation, and 119 were delivered at term. Ages varied from 14 to 40 years. Fifty-seven were primigravidas, 37 secundigravidas, 19 tertigravidas, and 21 of greater gravidity. The total length of labor varied from one hour and thirty-six minutes to seventy-three hours and forty-five minutes, and the third stage from three to ninety minutes, with an average of thirteen minutes. The placenta separated by the Schultze mechanism in 87 cases, Duncan in 34 cases, and was manually removed in 13 instances. The placenta was reported as questionably incomplete in only seven instances. Of these the placenta separated by the Duncan mechanism five times, and was manually removed twice. The postpartum temperature prior to operation was afebrile in 35 cases, Zone 1\* in 73 cases, and Zone 2† in 26 cases. Evacuation and packing were performed on the fifth to the eighteenth day post partum, usually on the tenth or eleventh day. Following operation the temperature was afebrile in 89 instances, and Zone 1\* in 37 instances. Elevation persisted for but two days in 22 of the patients, and three days in 9 cases. Eight operations were followed by a Zone 2† temperature. Three of these patients were in Zone 2† for but two days, and in one of these a Bartholin cyst was removed at the time of evacuation and packing. Two had elevated temperature for five days, one of these reached Zone 2† prior to operation. The other had endometritis, severe anemia, and hemorrhage, necessitating evacuation and packing of the uterus on the thirteenth day. The sixth patient was febrile for seven days. She had been delivered of twins and developed a septic temperature further complicated by profuse bleeding on the sixth day. The remaining two patients bled excessively. One required hysterectomy several hours after evacuation and packing. Both needed transfusions of blood and/or plasma. These patients were in the hospital twenty-eight and seventeen days, respectively, following operation.

The average hospital stay of the 134 patients was 17.9 days. Deliveries were: spontaneous, 48; low forceps, 61; midforceps, 6; version and extractions, 10; and breech extractions, 6. There were three sets of twins, four stillborn infants, of which two were macerated, and two neonatal deaths. It seems, therefore, that age, multiparity, length of labor, particularly of the third stage, method of delivery, mechanism of separation of the placenta, multiple pregnancy

\*Zone 1.—Temperature above 99° F. and below 100.4° F. for any two consecutive twenty-four-hour periods, exclusive of the first twenty-four hours.

†Zone 2.—Temperature of 100.4° F. or above for any two consecutive twenty-four-hour periods, exclusive of the first twenty-four hours.

or viability of the child, are not important factors as regards the occurrence of late postpartum bleeding.

The pathologic report on the tissue removed was degenerating decidua-like tissue, degenerating placenta, chronic metritis, chronic interstitial endometritis, or necrotic debris. The fact that true degenerating placenta was found by the pathologist in only 10 instances lends support to Rutherford and Hertig's concept that one of the important causes of late postpartum bleeding is failure of involution of the placental site itself without retention of placental tissue.

### Discussion

Because we feel this problem of continued postpartum bleeding sufficiently important, we have dared to violate orthodox concepts. When the lochia rubra persists more than six or seven days, more can be learned than risked by vaginal examination. There is also definite evidence that the open uterine wound is sealed off in approximately five days, and the mucosal surface is well on the road to complete regeneration. Furthermore, a vaginal examination is of prognostic value in that it serves as a deterrent for further manipulation if it produces a marked febrile reaction.

Whether or not evacuation and packing of the uterus in the relatively early puerperium are safe must be decided on the basis of results. However, if dilatation and curettage for retained secundines are performed almost routinely following abortions, as is recommended by DeLee, why should not evacuation be performed in the puerperium when there is known retained tissue? With the availability of penicillin for prophylactic or curative use, we feel we are on even safer ground.

The criticism that the amount of tissue evacuated is often very small can only be answered by the smooth and rapid convalescence which has followed its removal. On the other hand, is it not possible that the removal of infected tissue may prevent trouble in future pregnancies? We recall one patient who refused operation following diagnosis of retained tissue. Despite a persistent bloody discharge she became pregnant before many months, and terminated her pregnancy with a partial placenta previa. Whether there was any connection in this case can only be surmised. What we do know is that we have had no further trouble with any patient treated according to our routine.

### Conclusions

1. Despite conservative handling of the third stage of labor and careful examination of the placenta, the occasional retention of small pieces of placental tissue cannot be prevented or even detected at delivery.

2. Subinvolution of the placental site without retention of placental tissue is often a definite cause of postpartum bleeding.

3. Lochia rubra persisting beyond the seventh day, subinvolution of the uterus, and low grade temperature usually indicate retained placental or infected decidua tissue.



4. Vaginal examination of patients with characteristic symptoms about the eighth or ninth postpartum day will demonstrate the presence of retained tissue or marked subinvolution of the placental site.

5. We advocate removal of such tissue a day or two later under anesthesia employing placental forceps, followed by packing of the uterus.

6. Results of a series of 85 private and 49 ward patients are presented.

7. We believe this procedure lessens the period of morbidity, eliminates a potential danger to the patient, obviates untold annoyance to both patient and physician, shortens hospitalization, and returns the uterus to a healthy status for future pregnancies.

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## A STATISTICAL STUDY OF THE CASES OF PLACENTA PREVIA OCCURRING IN THE JEWISH HOSPITAL FROM 1935 TO 1946

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IN RECENT years our management and results in cases of placenta previa have been so markedly different than in the past, that we considered it worth while to present a brief report on the subject. There has been a marked reduction in maternal mortality and an appreciable reduction in fetal mortality. These seem to be directly related to the high incidence of cesarean section and the frequent use of blood transfusions. In the past, section was resorted to in only a few selected cases and blood was given only when the blood loss was very severe. In the group of cases to be presented here, section was done in 60 per cent of all the cases, while transfusions were used very freely regardless of whether the case was treated by simple rupture of the membranes or by cesarean section. Our own experience and a study of the literature have convinced us that the replacement of blood lost in cases of previa is of crucial importance.

From January 1, 1935, to July 1, 1946, there were 37,688 deliveries in this service. Among these were 165 cases of placenta previa; an incidence of 1:228, or 0.43 per cent. There were 61 (37 per cent) primiparas, and 104 (63 per cent) multiparas. The youngest patient was 19 years, the oldest 40 years.

Previous bleeding, varying from slight staining to recurrent moderate bleeding was recorded in 64 cases. Of these 64 patients, 17 had been hospitalized once or more during the pregnancy. Membranes were intact in 149 cases, and ruptured in 16. Nine patients were admitted in labor and in 5 cases symptoms of previa did not present themselves until after the onset of labor. The varieties of previa were distributed as follows: central, 37; partial, or lateral, 73; marginal, 43. In 12 instances the degree of previa was not recorded. Of the 165 cases studied, 160 were admitted in good condition, 4 in fair condition, and only one in very poor condition.

### Management

Of 165 cases, 97 were handled by abdominal cesarean section, one by vaginal cesarean (vaginal hysterotomy), and 67 by the vaginal route. Forty-three patients were given transfusions, ranging from 500 to 3,400 c.c. of blood. In all, 60 transfusions were given.

The cases handled vaginally were treated as follows:

- Vaginal Hysterectomy	1 case
Nothing, or Rupture of Membranes	21 cases
Other Vaginal Methods	46 cases
(Bag alone, bag and version, or version-extraction)	

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### Morbidity

Of the 21 cases treated by simple rupture of membranes, 3 were morbid, or 14.2 per cent. Average number of days of morbidity was two.

Of the 46 cases handled by more complicated forms of vaginal delivery, 14 or 30.4 per cent were morbid. Average number of days of morbidity was 3.8.

Of the abdominal sections, 66 were classicals, 30 were low-flap, one was a Waters. Fifty-one of the 97 cases, or 52.6 per cent were morbid. Average number of days of morbidity was 4.1. There was no appreciable difference in morbidity between the classical and low-flap sections.

In 1936, Ronsheim reported 283 cases of placenta previa treated at our hospital from 1907 to 1935. The important statistical comparisons between this series and the one reported here are brought out in Table II.

TABLE II.

	MANAGEMENT			MATERNAL MORTALITY	FETAL MORTALITY
	GROUP I	GROUP II	GROUP III		
Ronsheim's Series 283	23.3%	65.7%	11.0%	5.3%	46.3% (stillbirths only)
Present Series 165	12.7%	27.8%	59.3%	0.6%	25.8%

In his paper, Ronsheim advocated termination of the pregnancy with the first episode of serious bleeding, and concluded that the bag was the ideal method of treatment. Both of these ideas are refuted by the more recent literature, as well as by our own results in the group of cases reported here.

Watson and Gusberg, in 1943, reported a small series of cases and concluded that the use of Voorhees' bag was dangerous and inefficient in the treatment of placenta previa. These authors felt that the only two efficient methods of treatment were rupture of the membranes and cesarean section.

Williamson and Greely, in 1945, reported 162 cases and were of the opinion that the best results from vaginal delivery were obtained in those cases in which the bleeding could be controlled by simple rupture of the membranes. Otherwise, cesarean section seemed to be the management of choice.

Yepes and Eastman, in 1946, conclude that abdominal delivery should be employed in all cases of this complication with the exception of marginal types in multiparae with vertex presentations.

Our own results, with the markedly improved fetal and maternal mortality, would lead us to agree with the conclusions of the above three groups of authors.

Heretofore there has been general agreement with Ronsheim's statement that the uterus should be emptied with the first episode of vaginal bleeding. More recently, MacAfee and Johnson, working independently, have advocated a waiting policy in many cases of placenta previa because they felt it would improve the fetal prognosis. Both papers contend that hemorrhage in placenta previa is rarely, if ever, fatal in the absence of vaginal manipulation; therefore they advocate a waiting policy with the hope of getting better fetal results. This is particularly true for those cases that are not yet viable. Eastman, in checking 304 cases of placenta previa, found no instance of fatal hemorrhage in the absence of vaginal manipulation. Eastman then concludes that a patient with placenta previa with a non-viable or questionably viable baby, can often be safely carried to viability, provided she is in a well-equipped hospital and under expert care.

## Fetal Mortality:

Babies alive and discharged	124 (74.2%)
*Stillborn	17 (10.1%)
*Neonatal Deaths	26 (15.5%)
	<hr/>
	167 (2 sets of twins)

TABLE I. MANAGEMENT AND FETAL RESULTS

NOTHING OR RUPTURE OF MEMBRANES 21 CASES (12.7%)	OTHER VAGINAL METHODS (BAG, VERSION, ETC.) 46 CASES (27.8%)	SECTIONS 98 CASES (59.3%)
Babies > 5 lbs. alive 12 (57.1%)	Babies > 5 lbs. alive 12 (26.1%)	Babies > 5 lbs. alive 77 (78.5%)
< 5 lbs. alive 6 (28.5%)	< 5 lbs. alive 5 (10.9%)	< 5 lbs. alive 10 (10.2%)
> 5 lbs. stillbirth or neo- natal death 0	> 5 lbs. stillbirth or neonatal death 9 (19.6%)	> 5 lbs. stillbirth or neo- natal death 2 (2.0%)
< 5 lbs. stillbirth or neo- natal death 3 (14.2%)	< 5 lbs. stillbirth or neonatal death 20 (43.5%)	< 5 lbs. stillbirth or neo- natal death 9 (9.1%)

Table I gives at a glance the method of management and the fetal results. This table illustrates rather strikingly that the best fetal results are obtained when either a very simple vaginal procedure, such as rupture of the membranes, is done, or when a section is done. In the first group, the fetal salvage is over 85 per cent; in the section group it is over 88 per cent. The highest fetal mortality is found in the group handled by either bag, bag and version, or version-extraction. In this latter group, the fetal survival rate is only 37 per cent. While it is true that this multiple procedure group has in it the highest number of babies under 5 pounds and this is partly responsible for the high fetal loss, it is only partially so; in the same group, the babies of 5 or more pounds have a survival rate of only 45.7 per cent. From this it is obvious that the multiple procedure method of handling placenta previa through the vagina is the important factor in giving the high fetal mortality.

## Maternal Results

There was only one maternal death in this group of 165 cases.

CASE REPORT.—Patient was a 39-year-old gravida vii, para iv, 32 weeks pregnant. Was admitted in 1937 with history of bleeding on and off for one month. A vaginal examination was done on the second day after admission when bleeding recurred. No placental tissue was felt at this time. A second vaginal done at a later time showed a marginal placenta previa. Upon further bleeding, a third vaginal was done and central placenta previa was diagnosed. Membranes were ruptured and a bag inserted through the placenta. Bag expelled 49 hours later and a hand and cord prolapsed; temperature at this time was 103°, pulse 130. A version was done and spontaneous delivery followed 10 minutes later. Patient died of sepsis on the 12th day after delivery. A positive blood culture for streptococcus viridans was obtained during the illness. Patient also had a toxic anuria with a urea nitrogen of 153. She received sulfanilamide; 300 c.c. of blood on the 9th day and 500 c.c. on the 10th day.

\*Thirteen were 28 weeks or less.

3. The reasons for the marked improvement in fetal and maternal mortality, we believe to be the greater number of cases that were handled by either simple rupture of the membranes or cesarean section, and also to the more frequent use of blood transfusions.

4. The hydrostatic bag, or the bag followed by other vaginal manipulations, is not a good method for treating placenta previa. We predict that it will eventually be discarded completely.

5. The suggestions of Johnson and MacAfee to temporize in certain cases of placenta previa is worthy of trial. It should lower the fetal mortality.

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## Discussion

Most textbooks on obstetrics agree that the management depends upon the type of previa, the parity of the patient, the condition of the cervix and whether or not the patient is in labor. The type of previa is often difficult to determine accurately because it depends upon the amount of cervical dilatation. Theoretically it is impossible to determine the exact degree of previa until full or almost full dilatation has occurred. For this reason, most statistical tabulations, including our own, as to the type of placenta previa, are unreliable. All agree that central previa, in primiparas or multiparas should, with almost no exceptions, be handled by section. Some go further and state that all previas in primiparas, except the marginal variety, should be handled by section.

Some few observers advocate the use of the bag, but this is often followed by other operative vaginal procedures with the attendant dangers of laceration, hemorrhage and infection. The recent literature and our own results prejudice us against the use of the bag.

All agree, however, that blood should be used freely to replace blood loss regardless of the variety of previa, the parity of the patient or the method of management. Forty-three of our patients were given transfusions, from 500 to 3,400 c.c. In all, 60 transfusions were given. In recent years, all patients were given Rh negative blood. Most observers advise a gentle vaginal examination to be certain of the diagnosis, while some few are against it. We feel that in the vast majority of cases, a gentle vaginal done under strict aseptic precautions, with the operating room ready for possible section, can and should be done. In our series of 165 cases, 98 had vaginal examinations while 67 did not.

The time to terminate the pregnancy in cases of placenta previa is still a moot point. Until recently, the teaching by most authorities has been that the uterus should be emptied as soon as a diagnosis of placenta previa was made. The recent papers by Johnson of Texas and MacAfee of Belfast, Ireland, and the comments upon them by Eastman, seem to indicate that it is probably safe to temporize in some of the nonviable or near viable cases provided they are under good care in a well-equipped institution where they can be watched closely and blood loss can easily be replaced. This should bring about considerable improvement in the fetal mortality.

Our results in the group of cases herein presented have convinced us that the best results follow either simple rupture of the membranes or cesarean section. Practically the same conclusions were reached by Watson and Gusberg; Yepes and Eastman; and Williamson and Greely.

## Conclusions

1. We have presented a brief review of 165 cases of placenta previa with a fetal mortality of 25.8 per cent and a maternal mortality of 0.6 per cent.
2. This group of cases is compared with a previous series of 283 cases reported from our hospital 10 years ago with a fetal mortality of 46.3 per cent and a maternal mortality of 5.3 per cent.

Klebs-Löffler bacillus in the vagina. Doubt was cast on these findings by Lonne and Meyeringh, who were unable to demonstrate the bacilli in a single case in a series of 42 women. Suspicious organisms were found which, on closer examination, turned out to be pseudodiphtheria bacilli. Stander, in his text, states that he has never been successful in confirming Wauschkuhn's findings.

There is little in the literature regarding the effect of pregnancy on the course of diphtheria. Canéva, in 1852, described five cases of croup, three occurring in pregnant women. He commented on the rarity of laryngeal diphtheria in the adult, and felt that pregnancy was conducive to this form of the disease. Ollier, in 1904, stated that pregnancy did not predispose to or aggravate diphtheria. Labor was also innocuous. Berkeley, Bonney, and MacLeod state that pregnancy accentuates diphtheria, causes more laryngeal involvement, and results in a high maternal mortality rate in the absence of antitoxin therapy. Recently Kennedy described a case of laryngeal diphtheria in a pregnant woman. Most of the textbooks state that severe diphtheria results in abortion or premature labor, and Priestley stated that diphtheria was inimical to pregnancy. Ollier felt that untreated cases resulted in abortion, but the use of antiserum produced a significant decrease in the abortion rate. Döderlein was of the opinion that the toxin was responsible for abortion. Halban and Seitz cite an abortion rate of 33 per cent, which they feel is attributable to the effects of the toxin and anoxia. DeLee and Greenhill also quote a 33 per cent abortion rate and indict the toxins of the disease and respiratory disturbances. The source reference for this high abortion rate appears to be Anderodias who (quoting Halban) arrived at this figure through clinical observation and then confirmed it by injecting toxin intradermally into pregnant rabbits and causing similar abortion rate. There is no evidence that diphtheria produces congenital anomalies analogous to those produced by virus diseases such as German measles.

Stoeckel stated that if abortion or premature labor did not occur, the newborn was immune to diphtheria. Ollier noted that in certain cases the child of a diphtheritic mother was not born immune. Ribadeau-Dumas and co-workers demonstrated that immunization of mothers with anatoxin was ineffectual as a prophylaxis against diphtheria in the newborn. They also felt that infants under four months were refractory to immunization. Bourquin and Richardson proved the passage of antitoxin across the placenta, and more recently Liebling and his associates have clearly shown that active immunization of mothers with toxoid during pregnancy raises the fetal antitoxin titer, which reaches equal concentrations in mother and infant, and that the latter is in all cases Schick negative at birth. Brescia emphasizes that the frequently held concept that all infants are practically immune to diphtheria at birth is fallacious, and only infants born of immune mothers are themselves immune. Infants of these mothers give a negative Schick test in 100 per cent of the cases. However, at six months 80 per cent have become Schick positive. Infants born of nonimmune mothers show 50 per cent positive Schick reactions, and after four months are 100 per cent Schick positive. Fifty per cent negative Schick tests in the latter group may possibly be explained on the basis of poor skin reactivity shortly after birth, while the well-known unreliability of the Schick test in the newborn may lead one to question the findings in the former. Substantiating Ollier's statement that not all infants of diphtheritic mothers are immune are the case reports of Voron, Lyonnet, and Contamin, and Fleming. The French case report describes a 35-year-old woman who died shortly after her arrival at the hospital. Autopsy revealed tracheobronchial diphtheria. The patient, a para ix, had delivered a normal 3,050 Gm. female infant on the preceding day, which appeared healthy until the twelfth



## THE EFFECT OF DIPHTHERIA ON PREGNANCY, WITH A REPORT OF FIVE CASES

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THE occurrence of diphtheria during pregnancy or the puerperium is rare, as evidenced by the paucity of reports in the literature. There is a two-fold explanation for this. First, diphtheria is primarily a disease of the first decade of life; and second, the general practice of active immunization has resulted in a decreasing incidence of this disease during the present century. Recently, however, for reasons not yet clear, there has been an increase in the incidence of adult diphtheria. Thus, during the past year four patients with antenatal diphtheria have been observed. These women, with a fifth patient who was delivered in the Johns Hopkins Hospital in 1907, comprise the cases reported in this paper and represent the total number of patients with diphtheria in pregnancy seen in the Obstetrical Clinic in the past fifty years, during which time more than 50,000 deliveries occurred.

Contemporary obstetric textbooks have little to say concerning the occurrence of diphtheria in pregnancy and, in general, reflect opinions current in the older French and German literature. The most detailed coverage of the subject appears in Halban and Seitz.

The clinical and pathologic changes of diphtheria are well known. The localized lesions found in the female genital tract are less familiar. These latter constitute in a large measure a puerperal disease and are usually secondary to nasopharyngeal contamination, though primary diphtheria of the vagina may occur through cross infection where the bacilli may be carried from one patient to the other. Bumm, in 1895, first described the familiar adherent gray membrane in the vagina from which a pure culture of Klebs-Löffler bacilli was obtained. In 1898 Williams reported a case from this hospital involving the vulva. No other instance of localized diphtheria in the female genital tract has been seen in this Clinic during the present century. Sporadic reports have, however, appeared throughout the years. All agree that the disease generally appears in the puerperium, and is usually mild and responds readily to antitoxin therapy. It is, however, possible to have systemic involvement with paralysis in neglected cases. Local penetration of the uterus with spread to adjacent structures is practically nonexistent. In 1928, LeFevre reported an authentic case of diphtheritic endometritis following criminal abortion. LeFevre also reviewed at this time three other possible cases found in the literature. Investigations to determine the importance of the vagina as a carrier site for virulent bacilli have resulted in conflicting results. Wauschkuhn, routinely culturing the vagina of 200 pregnant women, discovered the diphtheria bacilli in 11 women. Four of these 11 women gave birth to infants with nasal diphtheria. Lietz found an even higher incidence. Broer claimed that 7 of 30 women examined in the Mainz area harbored the

for Klebs-Löffler bacilli but cultures from the other sites involved were negative. She was given 60,000 units of antitoxin, and 30,000 units of penicillin every three hours and neosynephryn nose drops. Examination of the abdomen revealed an estimated 1,000 Gm. fetus in left occipitotransverse position, with the fetal heart in the left lower quadrant. Progress was slow, but by January 21 cultures of the throat were negative for diphtheria bacilli. Shutting off the tracheotomy tube was intolerable. She was given local radium treatment to the hypertrophied pharyngeal lymphoid tissue, and late in January began to tolerate some plugging of the tracheotomy tube. On March 9, tonsillectomy, adenoidectomy, and bilateral myringotomy were performed. She fell into labor spontaneously on April 10, and after an eleven-hour labor delivered an infant weighing 2,960 Gm., which was in good condition. The puerperium was uncomplicated, and the patient and her baby left the hospital in good condition in June, except for the fact that the tracheotomy tube was still in place.

CASE 3.—(No. 375518.) The patient was a 20-year-old para 6-5-1-0-4, whose expected date of confinement was Nov. 21, 1946. On April 17, 1946, the patient's 2½-year-old daughter died of diphtheria. Two weeks prior to this her 4-year-old son had had a sore throat for three days. The patient had never received any toxoid or antitoxin. She was admitted on April 19, 1946, with a history of sore throat and nausea and vomiting for three days. During the preceding twenty-four hours she had experienced great difficulty in swallowing. On admission her temperature was 100° F. She had large, inflamed tonsils, and both were covered with adherent, grayish membrane. Pharyngeal culture was positive for Klebs-Löffler bacilli. Her electrocardiogram was normal. She received 80,000 units of antitoxin intramuscularly, 80,000 units of penicillin every three hours, and 100 mg. of ascorbic acid twice a day. She responded promptly, and on April 24 the membrane had disappeared, the temperature was normal, and penicillin was discontinued. The first negative cultures were obtained on May 1, 1946. Pelvic examination was first done on May 7, and revealed an estimated twelve weeks' pregnancy with the uterus rising to four fingerbreadths below the umbilicus. During the patient's course in the hospital she had no abdominal cramps or bleeding. On May 20, 1946, she developed partial palatal paralysis. This, however, disappeared, and she was discharged on June 6, 1946. She was delivered spontaneously of a 3,540 Gm. female infant on Nov. 18, 1946. Both the patient and her child did well.

CASE 4.—*Sydenham History No. 34089*: The patient was an 18-year-old primipara whose expected date of confinement was May 29, 1946. Her prenatal course was uneventful. On April 23 the patient developed a sore throat, and was hospitalized at another hospital where she was treated with penicillin without results. On April 29, cultures revealed Klebs-Löffler bacilli. She was given 80,000 units of antitoxin and transferred to Sydenham Hospital. She had never received toxoid. On admission she was moderately ill with gray adherent membrane over both tonsils. Temperature was 98° F. The uterus was one fingerbreadth below the xiphoid, and a fetus estimated at 2,400 Gm. lay in left occipitotransverse position with the fetal heart in the left lower quadrant. Five days after admission the throat culture was negative and sterile vaginal examination was carried out. The cervix was long, closed, and the pelvis was measured as normal. Electrocardiogram revealed a depression of the S.T. segments, and this was regarded as evidence of beginning myocarditis. On May 12 the patient began to develop palatal paralysis and difficulty in accommodation. She fell into labor spontaneously on May 29, and after a moderately difficult labor characterized by uterine inertia she was delivered by low forceps of a 2,820 Gm. infant which was in fair condition.

day post partum, at which time she became febrile, developed coryza, otitis, and umbilical infection. A few days later the infant died of diphtheria. Fleming's case reveals that the mother became ill two days before delivery. On the day after delivery she was admitted with oral, vulvar, and anal diphtheria. Antitoxin therapy resulted in recovery. On the seventh postpartum day the baby was admitted with faucial diphtheria. Antitoxin therapy was again successful. Both cases indicate that the disease occurred so late in the pregnancy that there was insufficient time to build up an antitoxin level which would cross the placental barrier. As a result both infants were nonimmune.

The experience of the Johns Hopkins Hospital Department of Obstetrics with this disease follows in detail.

CASE 1.—(No. 20555.) A 20-year-old single Negro woman was first seen in the Outpatient Department on Sept. 20, 1906. Although her expected date of confinement was calculated to be in February, 1907, the pregnancy appeared to be slightly more advanced, and she was thought to be due in January, 1907. Her prenatal course was uneventful until Dec. 22, 1906, when the patient first complained of headache and sore neck. On December 23, her temperature was 101, her pulse 104, and her throat sore. She had a small white membranous patch on the soft palate and the tonsils and pharynx were diffusely injected. Culture revealed Klebs-Löffler bacilli, and the patient was given 1,500 units of antitoxin. On December 24, an additional 1,500 units were given, and the patient felt much improved. Her temperature was 98 and pulse 74. By December 30 the membrane had disappeared and the patient was asymptomatic. Cultures of the throat were negative. There were never any signs of cardiac, neurological, or renal involvement. The urine was constantly negative. Pregnancy proceeded uneventfully. On January 29 the patient went into labor spontaneously, and was delivered under chloroform anesthesia of a normal female infant weighing 2,980 grams. The puerperium was uncomplicated, and the patient was discharged on the tenth postpartum day. The baby was in excellent condition and weighed 3,220 Gm. at discharge.

CASE 2.—(No. 372477.) A 20-year-old white married para 2-2-0-0-2, whose expected date of confinement was April 6, 1946, was admitted to the Johns Hopkins Hospital on Jan. 7, 1946, breathing noisily through a tracheotomy tube. Her family history was noncontributory. She had never received diphtheria toxoid. The present prenatal course had proceeded normally until one month before admission, when the patient developed otitis media requiring left myringotomy. Purulent material had been draining from the left ear ever since. About three weeks before admission, labored respirations and lacrimation of the left eye began. Two days before admission the patient lost her voice and was seen in a hospital in Miami. The vocal cords were covered with a fibrinous exudate, and a pneumococcus grew out on culture. The patient was advised to seek help in a larger medical center. She was flown to Baltimore aboard a C-47, which fortunately carried a medical officer. Over Charleston, South Carolina, the patient developed complete respiratory obstruction, and an emergency tracheotomy was performed in midair. On admission the temperature was 99.8° F., pulse 112, and respirations 24 and noisy. Blood pressure was normal. Physical examination revealed complete nasal obstruction. Anteriorly in the nasal passage was a whitish membrane. The pharynx and tonsils were diffusely injected, and the tonsillar nodes were enlarged and tender. The tracheotomy tube was functioning well. Both ears drained purulent material. The fundus rose to one fingerbreadth above the umbilicus, and the fetal heart was present in the left lower quadrant. Pharyngeal culture was positive

animals, injected large doses of diphtheria toxin subcutaneously. These invariably killed the animals. Autopsy findings in the fetuses and mothers showed identical findings, namely, parenchymatous and fatty degeneration of the organs, and hemorrhage in the adrenals. When smaller doses were used, no pathologic changes were noted in the fetal organs, though the maternal organs were characteristically affected. Using even greater massive doses, he injected guinea pigs at term and performed cesarean sections upon them six to twelve hours later. Following this, he injected large doses of the fetal serum into other pregnant guinea pigs, with death and typical pathologic changes ensuing in both the maternal and fetal organs. These experiments seemed to prove conclusively in the guinea pigs that toxin does pass the fetal barrier. This work could not be substantiated by Nattan-Larrier, Ramon, and Grasset, who injected term rabbits with 15 c.e. of toxin (1/400 c.e. lethal to the guinea pig). Eight hours later cesarean section was performed and a living litter obtained. Two c.e. of the serum of these fetuses were then injected into guinea pigs with innocuous results, while 1 c.e. of the mother's serum proved fatal. Similar results were obtained using guinea pigs as test animals. Furthermore, typical adrenal gland changes produced by the toxin in mothers were lacking in the fetus. To prove fetal immunity was passive, these same investigators injected 2,000 Ehrlich units of antitoxin intravenously into rabbits at term. Delivery occurred the following day. Following delivery, 1 c.e. of maternal serum neutralized 80 MLD of toxin, while 1 c.e. of fetal serum neutralized 25 MLD of toxin. Therefore, these investigators concluded that the placenta is permeable to antitoxin, but impermeable to toxin. Confirmation of the above findings was reported by Mouriquand and his co-workers, who injected 12 term guinea pigs with toxin. In the guinea pig, toxin produces hemorrhagic changes in the adrenals with marked decrease in adrenalin and cholesterol content, the maximal effect being reached in sixteen hours. After sixteen hours the animals were sacrificed. All the mothers exhibited typical adrenal changes, while none of the offsprings' adrenals was affected. It should be noted at this point that the placentas of guinea pigs and term rabbits are hemoendothelial, and, as such, are more permeable than the human placenta which is hemochorial. Clinically, the nonpassage of toxin in man is evidenced by the fact that not a single case appears in the literature of a child having been born with diphtheritic myocarditis or diphtheritic paralysis. The available evidence seems to point definitely to the placenta as an effective barrier against the passage of toxin. While our Case 4 did exhibit palatal paralysis for a short time and might prove to be an exception to this rule, it was the feeling of all observers that the rapid recovery and general flaccidity of this infant at birth would seem to indict the long labor and difficult delivery rather than diphtheria toxin in the fetal blood.

In the reported cases, pregnancy did not seem to alter the course of the disease in any way, nor in the few cases here reported did the disease seem to alter the course or the outcome of pregnancy. Such cases should be treated in manner similar to diphtheria in the nonpregnant individuals. Antitoxin is the single most important therapeutic agent. Secondary infections can be

Twenty-four hours after birth the infant exhibited some regurgitation of food when feeding was attempted. There was unilateral impaired palatal action. An electrocardiogram of the infant showed no abnormality. Twenty-four hours later the palatal paralysis disappeared. The infant had less than 1/1000 unit of antitoxin per c.c. of blood, though the mother was Schick negative. It was therefore given 20,000 units of antitoxin prophylactically and was separated from its mother. The initial difficulty in swallowing was considered not to be due to the effect of the diphtheria toxin, but rather an expression of the general muscle flaccidity following a slightly difficult delivery and prolonged labor. The patient left the hospital on her tenth postpartum day. At this time the infant was in good condition.

CASE 5.—(No. 390965.) The patient was a 28-year-old white para 4-3-0-1-3, whose expected date of confinement was December 16, 1946. The present illness began with headaches on May 11, and on May 14 she developed sore throat and painful swallowing. She was treated with sulfadiazine and penicillin without results, and entered Sydenham Hospital on May 16. On admission her temperature was 100° F. She did not appear to be acutely ill. The tonsils were enlarged and injected. There was a grayish membrane over the left tonsil anteriorly. There was some membrane also on the posterior pharyngeal wall. Abdominal examination revealed a fourteen weeks' pregnancy with the uterus rising to three fingerbreadths below the umbilicus. Throat cultures taken on May 16, 17, and 18, were positive for Klebs-Löffler bacilli. Pelvic examination at this time confirmed the diagnosis of pregnancy. The patient was treated with 40,000 units of penicillin every three hours. In addition she received 100,000 units of antitoxin intramuscularly, and 100 mg. of ascorbic acid twice a day. Following the administration of the antitoxin the temperature rose to 103° F., but subsided rapidly. One week later the patient began to run daily temperature elevations to 101° F. and 102° F., and on May 27 she developed joint pains, and an urticarial rash appeared over her body. The membrane disappeared from her throat on May 21. On June 11 the electrocardiogram revealed a decreased amplitude in all levels, and it was felt that she had a mild myocarditis. In spite of the serum sickness, her pregnancy progressed uneventfully.

The patient was readmitted in July, 1946, with peripheral neuritis involving the lower extremities. She was treated with bed rest and thiamin, and was discharged after three weeks, greatly improved. Her pregnancy progressed normally during this admission.

She was delivered of a 4,020 Gm. male infant in good condition on Dec. 26, 1946. Both mother and child did well and were discharged from the hospital on the sixth postpartum day.

### Discussion

A fundamental question in regard to this complication of pregnancy is whether the diphtheria bacilli and/or its toxin pass through the placental barrier. No one has ever succeeded in demonstrating the Klebs-Löffler bacillus in the placenta, and congenital transmission of this disease has never been proved. The organism has never been shown in fetal blood. Needham states that with very few exceptions toxins and antigens do not pass through the placenta. On the other hand, the placenta is readily permeable to antitoxin. Therefore, immunity in the fetus at birth, if present, is always passive and transitory. Schmidlechner, in 1904, however, using term guinea pigs as test

## EXTRAPERITONEAL CESAREAN SECTION; INTRAPERITONEAL APPROACH

### Presentation of the Author's Technique

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MUCH of the progress in the development of the lower uterine segment types of cesarean section has occurred in the past twenty-five years. The Waters' supravescial, the Norton paravesical extraperitoneal, and the Smith modification of the Veit-Fromme-Hirst exclusion transperitoneal cesarean sections, are striking examples of recent advances. Any operation which successfully excludes the peritoneal cavity is a step forward. The Smith operation, although safer than the intraperitoneal cesarean, two-flap type, in potentially infected cases, certainly cannot compete with the Waters' or the Norton truly extraperitoneal cesarean sections. In frankly infected cases, i.e., placental site infection, metritis, etc., no type of cesarean section is safe. This has been stressed again only recently by Norton. The Porro, modified as a total abdominal hysterectomy, is the operation of choice in these surely infected cases.

The Smith operation of peritoneal exclusion, although cleverly planned and executed, has some advantages and some disadvantages. While it does afford a more roomy and elastic area than some of the other exclusion operations, the area exposed is still too limited. It is more time consuming. The peritoneal apron is not intact; in fact, it is rather extensively cut. In the process of extracting the baby, the peritoneal apron is more likely to be further traumatized than it would be in those cases where the apron is left intact, i.e., Waters, Norton, Ricci, Latzko. The abdominal cavity must be excluded by a long line of sutures, all of which must perforate the peritoneal cavity which we had hoped to exclude. Furthermore, after the delivery of the baby, the suture line becomes quite distorted and allows for later seepage.

The present widely performed intraperitoneal, retrovesical, two-flap type operation has been so popularized that the low Sanger incision and the high classical incisions are rapidly becoming obsolete. Despite the greatly improved results obtained by this popularization of the intraperitoneal low cervical operation, it has certain disadvantages which can be eliminated. With this in mind, the writer proposes for consideration a type of cesarean section which aims to expose the retrovesical and intraperitoneal portion of the lower uterine segment by utilization of a small incision into the peritoneal cavity just above the abdominovesical reflection of peritoneum. Nothing of an original nature can be claimed for this method, since it utilizes principles already set down by Latzko, Ricci, Waters, Norton, and many others. It does, however, claim to be an improvement over the highly favored intraperitoneal lower segment operation which utilizes two flaps of peritoneum. The extraperitoneal enthusiasts claim that their techniques are not difficult to perform, yet, even in their expert hands,

controlled by chemotherapy and antibiotics. Myocarditis, of course, should be treated by bed rest. Although the reported abortion rate in diphtheria is 33 per cent, no interruption of pregnancy was observed in our cases, and none of them showed any premonitory signs of miscarriage. Abortion in acute infectious diseases with high fever, however, is not uncommon, and it is conceivable that inadequately treated diphtheria might result in a high abortion rate.

### Summary

1. A review of the literature of diphtheria in pregnancy is presented.
2. Five instances of diphtheria in various stages of pregnancy are reported.
3. There is no indication from these cases that adequately treated diphtheria increases the incidence of abortion or premature labor.
4. No evidence was found in the literature nor was any obtained from these cases that might indicate the passage of diphtheria toxin across the placental barrier.

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## DYSGERMINOMA OVARIUM

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ALTHOUGH fifteen years have elapsed since Robert Meyer enriched our knowledge of ovarian tumors, opinion still is divided both with regard to the degree of malignancy of dysgerminoma of the ovary and the nature of its surgical management.

Of course this difference may in part be attributed to the comparative rarity of this special pathologic growth, but since about 250 cases have already been reported in the literature and many other observed cases no doubt remain unpublished, the concerned problems become one with which every physician should be thoroughly familiar.

It is, therefore, rather astonishing that in a number of surgical textbooks which have appeared within the past two or three years, this subject is wholly ignored, while in others the authors are at variance regarding the nature and management of this form of ovarian neoplasm. As something unique, mention should be made of the fact that Bourne<sup>1</sup> in his "Synopsis" makes this astounding statement under the heading dysgerminoma, which he correctly classifies among sex-cell tumors of the ovary: "Benign in female, malignant in male. Bilateral in women. Chiefly found in young women."

We shall show that the author is in total error, and that such teaching of undergraduates may eventually lead to disastrous consequences.

### Abstracts From the Literature

In view of the above statements it may not be amiss at this place to cite a few of the many contributions to the literature in this particular field.

Dworzak,<sup>2</sup> in 1935, reported the case of an 18-year-old girl with unilateral dysgerminoma for which he extirpated the right ovary and tube with the growth. There appeared a recurrence in the left adnexa, which responded to radiation. Three years earlier this author had operated conservatively on four older women and all these patients died.

Novak and Gray,<sup>3</sup> in 1936, reported their exhaustive study of 17 cases, and reached the conclusion that dysgerminoma is a highly malignant tumor compelling disregard of future pregnancy. These authors decided that radical operation is the indicated method of managing this type of tumor and not mere unilateral extirpation with subsequent radiotherapy.

Foderl,<sup>4</sup> in 1938, reviewed 13 cases and reached virtually the same conclusion as that of Novak and Gray. He urged radical intervention because the prognosis is very grave.

Seegar,<sup>5</sup> in 1938, contributed a study of no less than 79 cases, most of the concerned individuals being under 20 years of age and without any evidence of pseudohermaphroditism. He found that the mortality rate ranged between 35 and 60 per cent, depending upon the character of the surgical procedure employed.



Russell,<sup>6</sup> in 1938, published his experience which contained a valuable lesson. In one instance out of seven there was a unilateral dysgerminoma and this woman died as a result of recurrence in the opposite ovary.

Stoia and associates,<sup>7</sup> in 1930, reported three cases of dysgerminoma. In these death took place as a consequence of metastases.

Sailer,<sup>8</sup> in 1940, published five cases in which the ages ranged between 10 and 21 years. In four of these the dysgerminoma attacked the right ovary, and only in one was the neoplasm found on the left side. After conservative operation one of the patients died after a year, while the others remained under observation.

As stated above, it is not my intention to review the entire literature on dysgerminoma of the ovary, but it is palpable from the few above abstracts that we are dealing with a problem meriting serious consideration of several involved factors.

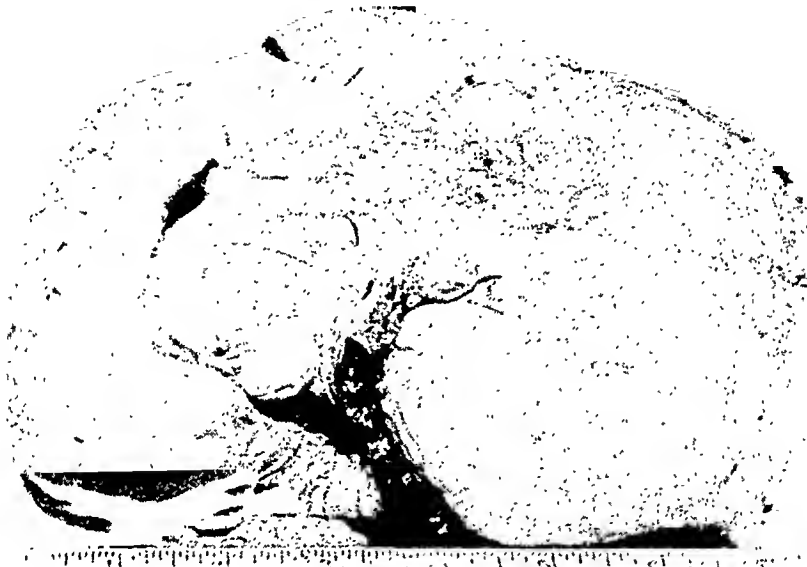


Fig. 1.

### Case Report

A single, white, 23-year-old woman was admitted to Edgewater Hospital in May, 1945, with a complaint of nocturia, diurnal polyuria, and of a rapidly growing mass in the lower left side of the abdomen. This condition was stated to have existed within the preceding six weeks.

The previous history has a bearing on the case only to the extent that it definitely establishes the time element of the present complaint. She had been recently hospitalized on two occasions; once in February for a submucous resection, and in March of the same year at Edgewater Hospital for a nasal hemorrhage. A general physical examination was made several days after her nasal operation, and another at Edgewater Hospital after her admission for the nasal hemorrhage. The records of the latter general examination contain absolutely nothing about the presence of a mass in the abdomen.

*Physical Examination.*—The patient was in every respect a normal, well-developed young woman, weighing 115 pounds and a height of five feet, two inches. The distribution of hair on her face, body, and pubes was normal. The hymen was intact. The mass, about the size of an eight months' pregnancy, filled the entire left lower half of the abdomen, extending about three finger-

breadths above the umbilicus. It was firm in consistency and gave the impression of being lobulated. Careful vaginal examination yielded little additional information. The introduction of a small speculum revealed a normal cervix, but rectal palpation showed the mass to occupy most of the left cul-de-sac, and confirmed the lobulated character of the growth.

*Past History.*—Her catamenia appeared at the age of eleven, was the 28-day type, with the flow lasting three days. The flow was rather scanty, but not associated with pain. She had undergone a tonsillectomy and a mastoidectomy about eight years ago. Her septal operation is mentioned above.

*Diagnosis.*—With flat x-ray films showing a massive shadow in the lower left abdomen and pelvis without the presence of any calcified areas, the diagnosis of left ovarian tumor became a certainty.

*Operation.*—Laparotomy through a low midline incision was performed on June 2, 1945. The section revealed a large amount of free fluid and a mass the size of an adult's head firmly embedded in the left pelvis. It was grayish in color resembling a brain, firm, and lobulated. It involved the entire left ovary (Fig. 1).

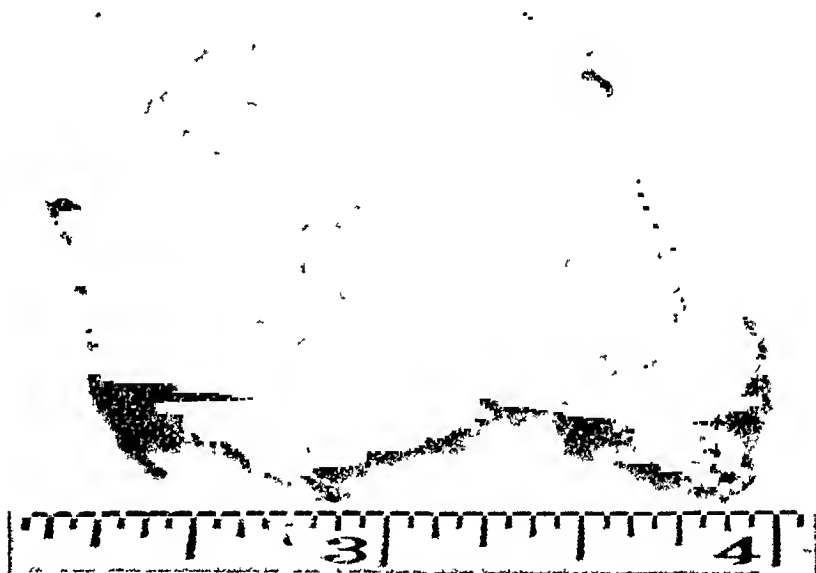


Fig. 2.

The broad ligament was about four times its normal thickness, and was intensely vascular. Further exploration revealed a similar but much smaller tumor, about the size of a hen's egg attached to the right ovary (Fig. 2). There was no involvement of the tubes, ligaments, uterus, or mesenteric glands. The liver, omentum, and other viscera appeared to be normal.

The left ovary and tumor were removed in toto. Without previous permission for more radical surgery, it was deemed advisable to restrict the procedure to removal of the major portion of the right ovary with the growth in order to gain time for microscopic study and, if need proved, to obtain consent for more radical surgery. We felt justified in this delay also clinically, because of the absence of metastases either in the pelvis or elsewhere.

The patient made an uneventful recovery and was temporarily discharged on the tenth postoperative day.

*Pathologic Report.*—(Path. No. 13095—Hosp. No. 68322). The specimen consisted of two ovaries and one Fallopian tube, the largest measuring 17 by

19 by 8 centimeters, to which was attached the left tube. The smaller ovary measured 4 by 4 by 2½ centimeters. The capsules of both ovarian masses were smooth and intact, grayish in color. The veins at the pedicle of the large tumor were greatly dilated and tortuous. Both tumors felt solid. The larger tumor cut with great ease and fragmented slightly. The cut surfaces presented a soft, easily fragmented stroma, red in color. The stroma had a mottled-gray appearance with some areas dark red and hemorrhagic, and others appearing

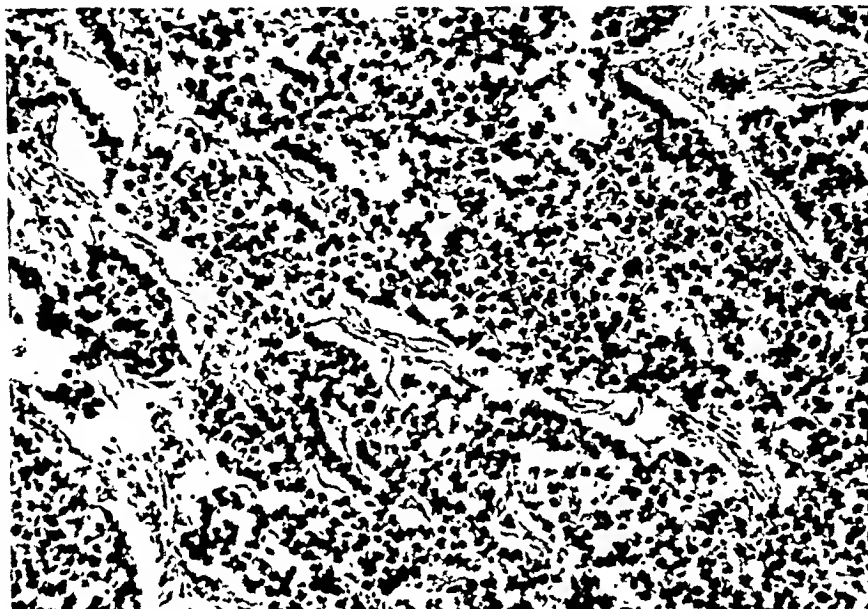


Fig. 3.

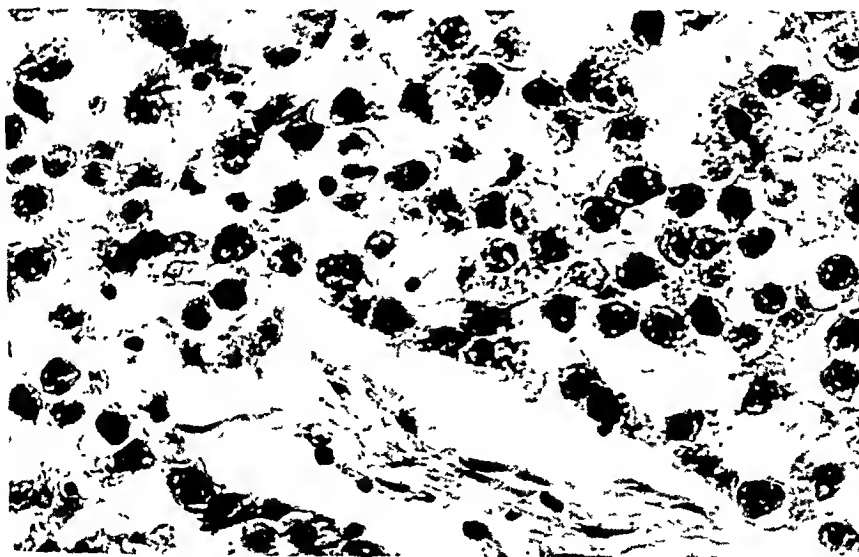


Fig. 4.

grossly to be necrotic and in some places liquefied. The smaller of the two tumors was covered by peritoneum and appeared to be complete. It had attached a small part of the ovary, was also friable, but presented a more homogeneous curly white cut surface. The Fallopian tube measured 8 centimeters in length, and revealed open fimbriated ends. There was no gross involvement of the tube.

*Microscopic Findings.*—The sections showed cords and nests of extremely pleomorphic and anaplastic cells throughout. They varied in size and staining

qualities with many evidences of mitosis. The stroma was extremely loose, and consisted of strands of fibrous tissue with areas of edema and hemorrhage. Scattered among the tumor cells were focal and diffuse accumulations of small round cells resembling lymphocytes. The Fallopian tube showed that the mucosa was partially filling the lumen and the muscularis. The tube proper was otherwise normal (Figs. 3 and 4).

*Pathologic Diagnosis.*—Dysgerminoma of ovaries.

*Second Operation.*—After explaining to the patient and her family the malignant character of the growths and the ultimate chances for recovery after a radical operation, consent was obtained and a second operation performed on July 5, about one month after the first procedure. This operation consisted of total extirpation of the uterus and remaining adnexa.

Again the patient made an uneventful and complete recovery. She sustained during her convalescence a slight disturbance of the urinary bladder as a result of catheterization, but was able to leave the hospital on the tenth postoperative day. The operation was followed by an intensive course of radiation. She also was given 10,000 units of theelin in oil every other day and one-half grain of phenobarbital three times daily to prevent any symptoms incident to her sudden artificial menopause. This regimen controlled the situation, except for periodic evidence of nervousness. In time the dosage of the medication could be reduced, and at the end of three months no further treatment proved necessary. To date of writing she has remained in a normal condition, free from any symptoms and able to pursue her daily work.

*Second Pathologic Report.*—(Path. No. 13115—Hosp. No. 69106). The specimen consisted of the uterus and cervix 8 by 4 by 3 centimeters. The cervical epithelium was smooth; the endometrium reached a thickness of 3 millimeters and was smooth. Attached was the right Fallopian tube measuring 8 centimeters in length and showing free fimbriated ends. Attached to the tube was the right ovary, 3 by 3 by 1.5 centimeters, containing corpus luteum and a hemorrhagic cyst as well as several small follicular cysts.

Microscopic sections of the right ovary showed the blood vessels to be markedly thickened with hemosiderin deposits in the stroma lining the wall of the cyst. Another section revealed many dilated blood vessels with hemorrhage into the surrounding stroma. A third section of the ovary contained a large hemorrhagic cyst with the stroma essentially unchanged. The Fallopian tube showed the mucosa partially filling the lumen of the muscularis. And a fourth section of the ovary showed hemorrhagic cysts in the stroma and corpora albicantia. Section of the uterus showed the endometrium to be markedly thickened, the glands elongated with the cell outline intact. There was fibrosis in the myometrium.

*Pathologic Diagnosis.*—(1) Fibrosis uteri; (2) hyperplasia of the endometrium; (3) hyperplasia of the mucosa of the Fallopian tube; (4) hemorrhagic cysts of the ovary.

### Comment

In the light of clinical experience and pathologic studies of dysgerminoma ovarii, there is no room for doubt that this neoplasm is highly malignant. As a corollary, its surgical management logically must be as radical as that of carcinoma of the ovaries.

Since the neoplasm attacks even the very young, it is but natural for humane surgeons to hesitate in carrying out an operation that precludes future pregnancy, especially when the capsule of the growth is unbroken. In such a

case one is tempted to restrict oneself to a conservative removal of the tumor, and to rely upon postoperative radiation to prevent metastases.

But once the diagnosis is made, the most pressing objective is not the conservation of potential procreative power, but the preservation of life itself. To this should be added that after a course of x-ray therapy ovarian function will be destroyed in virtually all cases.

Given a growth with an unbroken capsule, the diagnosis after its exposure is not always possible macroscopically, for which reason resort should be had to microscopic section of the removed growth, since the establishment of the correct diagnosis dictates the course to be pursued in the very young as well as mature patients. Certainly radical extirpation of the genital apparatus should be carried out only with the consent of the patients or their parents, but, when these are explained, the reason for the operation as a lifesaving measure, no difficulty will be experienced in most instances in obtaining such permission. In the very young a compromise may be effected by pointing out that every conservative intervention makes it incumbent to keep the concerned patient under observation in order to enable the surgeon to detect an extension of the growth or the appearance of metastases.

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## MEIGS'S SYNDROME; A CASE REPORT AND A REVIEW OF RECENTLY PUBLISHED CASES

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*(From the City Hospital)*

THE publication by Meigs and Cass<sup>1</sup> in 1933 of an article describing seven cases of ovarian fibroma associated with ascites and hydrothorax was a milestone in gynecology. Their original communication called attention to the fact that patients with what was subsequently termed "Meigs's syndrome" frequently present a clinical picture almost identical with that of far-advanced malignancy. They clearly stated that, in an occasional apparently hopeless case, though the surgeon must risk the dangers of a possible postoperative mortality, he may be rewarded by a most gratifying result. Meigs has emphasized this very important fact in all of his subsequent papers.<sup>2-4</sup> Unfortunately, while the medical world in general and gynecologists in particular are now thoroughly familiar with the symptom triad of Meigs's syndrome, there appears to be a lack of understanding of the primary purpose of his contributions on this subject.

By 1943, Meigs and co-workers<sup>4</sup> had collected 27 cases of the syndrome. Since that time 16 additional cases have been reported in the literature to which there is added the case detailed below. In his latest paper, Meigs tabulated the cases in a fashion similar to Table I. His table has merely been continued, in this way bringing the literature up to date. However, one column has been added to Meigs's table, i.e., the weight or size of the tumor.

All the cases reported by Meigs have been reviewed in order to establish the weight or size of each tumor. While the weights in many cases are not given, estimating them from the stated dimensions of the tumor, we may conclude that, with the exception of two, that of Bomze and Kirshbaum<sup>5</sup> and that of Mae Fee,<sup>6</sup> probably none of the others weighed more than 2,500 to 3,000 grams. The largest ovarian fibroma exhibiting the syndrome was found in the case reported by Bomze and Kirshbaum. This tumor, which weighed 7,150 Gm., was not removed at operation, due to the poor condition of the patient. Two days later the patient died, and it was recovered at autopsy.

In 1941, Mae Fee reported a case in which he removed a multilocular cystadenoma of the left ovary which weighed over 8 kilograms. This patient had fluid in the abdominal and chest cavities. She made an uneventful recovery from the operation. However, during her period of convalescence, it was necessary to do a thoracentesis. In 1945, Millett and Shell<sup>7</sup> reported the case of a large multilocular pseudomucinous cystadenoma extending to the umbilicus. The weight and size were not given. In this case, too, a postoperative chest tap was done. The authors of both of these case reports stated that they believed they were dealing with Meigs's syndrome. However, it is the opinion of the present author that the term "Meigs's syndrome" should be confined to

the triad of solid tumor of the ovary, ascites, and hydrothorax because: (1) It is so considered by the vast majority of physicians at all acquainted with it. (2) If the issue becomes clouded by including in this category tumors which are at least potentially malignant and primarily cystic in character, the important and definite understanding of the benignity of the whole syndrome will, in all probability, be lost. (3) The two cases mentioned above (Mac Fee, and Millett and Shell) failed in one important respect to conform to the typical clinical picture; that is, the chest fluid was not rapidly and spontaneously eliminated. In a private communication, Dr. Meigs states: "I don't think that papillary tumors or any kind of tumor that is not of the solid variety should be considered" (as cases of Meigs's syndrome).

The possibility of the diagnosis being missed in many cases must be considered, since Meigs operated on two patients exhibiting the syndrome within one year (1941).<sup>4</sup> After all, 1,000 to 1,500 c.c. of fluid in the chest cavity need not produce symptoms, and a rather thorough physical examination or chest x-ray would be necessary to establish its presence. No comment is needed as to the infrequency of either of these procedures on the average surgical service.

After a review of all cases of Meigs's syndrome, I would suggest that both ascites and hydrothorax probably appear only after the tumor has been present for some time. In other words, almost all cases of Meigs's syndrome thus far reported might be classified as neglected, or perhaps better to say unexamined, patients. From this we may further conclude that, were it not for the fact that vaginal examinations are so common today we would see many more cases in this category.

### Case Report

M. M., aged 55 years, white, para 0, gravida 0, single, was first seen on Sept. 3, 1944. She complained of a large mass rising from the groin and extending halfway to the knee. From the lowest part of the mass there was a constant discharge of clear, light yellow fluid. She stated that she had never before consulted a doctor. The family history and past surgical and medical history were negative. Her menses had ceased at the age of 47 years, and she had had an uneventful menopause, with no vaginal bleeding since that time. She first noticed a swelling in her right groin about ten years before. This had gradually increased in size until it finally reached almost to her knee. Approximately nine months prior to the time of her first examination, the lower part of this dependent mass had opened, allowing yellowish fluid to escape. After about six weeks this ceased, only to recur with an increasing amount of fluid two months prior to her visit to me. The patient complained of progressive weakness and complete loss of appetite with resultant muscular atrophy. The only other significant symptom was a nonproductive cough of increasing severity during the previous several months.

*Physical Examination* revealed a white, emaciated woman appearing considerably older than her stated age. Her weight was 108 lbs.; blood pressure, 190/110. The head and neck were essentially negative. The heart was enlarged concentrically with an apex rate of 100 per minute. The entire right chest to the axilla was flat on percussion, and only the most distant breath sounds were audible in this area. There was also some flatness at the left base. The abdomen was enlarged to the size of a full-term pregnancy and was filled with a hard, smooth, relatively freely movable mass which seemed to spring from the pelvis. The presence of ascites was demonstrated by a fluid wave and shifting dullness.

TABLE I. SYNOPSIS OF 17 ADDITIONAL

CASE AND DATE	SURGEON OR AUTHOR	AGE	STATUS	CHIL-DREN	CHIEF COMPLAINT
28. Dec., 1931	Healy <sup>4</sup>	48	S	0	Swelling in abdomen; shortness of breath; abdominal pain
29. Oct., 1941	Jones <sup>9</sup>	50	M	2	Loss of weight; weakness; shortness of breath on exertion; abdominal tumor
30. Nov., 1941	Perlmutter <sup>10</sup>	60	M	1	Shortness of breath for two years; pain in right chest for one month
31. Feb., 1942	Watson et al. <sup>11</sup>	75	M	5	Weakness; palpitation; ankle edema
32. Mar., 1942	Taylor <sup>4</sup>	72	M	6	Abdominal discomfort
33. June, 1942	Townsend <sup>12</sup>	49	S	0	Progressive abdominal enlargement; weakness; dyspnea
34. Aug., 1942	Bottaro <sup>13</sup>	58	M	1	Progressive abdominal enlargement; sudden onset five days before of flow of clear liquid from umbilical area
35. Sept., 1942	Kelemen <sup>14</sup>	49	M	3	Cough dyspnea; weakness; diaphoresis
36. July, 1943	Mendel and Tyrone <sup>15</sup>	44	S	0	Abdominal distention and pain
37. ?	Rubin et al. <sup>16</sup>	52	M	?	Irregular menses; abdominal enlargement
38. ?	Rubin et al. <sup>16</sup>	58	M	3	Dyspnea; leg edema; abdominal enlargement
39. Sept., 1943	Gardiner and Floyd-Hart <sup>17</sup>	38	M	0	Shortness of breath on exertion; back pains
	Gild <sup>18</sup>	30	M	0	Cough; shortness of breath; loss of weight for 2 months
40. ?					
41. Nov., 1943	Dockerty and Masson <sup>19</sup>	43	M	1	Mass in lower abdomen with gradual enlargement in past year
42. Recently	Baird <sup>20</sup>	59	S	0	Breathlessness and lump in abdomen for one year
43. Recently	Baird <sup>20</sup>	47	M	1	Breathlessness for five years
44. Sept., 1944	Simon	55	S	0	Mass in the groin and abdomen; weakness; loss of appetite

\*In this case the pathologist found bilateral papillary cystadenocarcinoma. However, the symptomatology and postoperative course was that of a typical Meigs's syndrome. The finding of a carcinoma in what appeared to be a simple ovarian fibroma was purely incidental. Three years postoperative the patient was reported to be in excellent health with no evidence of recurrence of the carcinoma.



the bladder has been cut, ureters injured, and the peritoneum buttonholed so frequently that their methods must be reserved for the obstetric surgeon who possesses better than average skill. The type of cesarean section here presented has served me well; the steps of the procedure are not difficult to perform; the operation can be mastered in a short time by the occasional operator; the procedure eventually familiarizes the operator with the exact anatomy of the pelvic fascias and the relationship and reflections of the overlying peritoneum so that when he is called upon to perform a truly extraperitoneal operation he will be better qualified; the operation, unlike the Waters' supravesical or the Norton paravesical extraperitoneal techniques, is a procedure that can be used electively in all patients who have not been in labor; the operation here recommended, while not intended to compete with the already almost perfect techniques of Latzko, Ricci, Waters, or Norton, can be kept truly extraperitoneal if the peritoneal incision is closed before the lower uterine segment is incised; and finally, it is claimed for this type of section: (1) relatively easy access is gained to the retrovesical, infraperitoneal area of the lower uterine segment, with less danger of repeatedly buttonholing the peritoneum, injuring the bladder, ureters, or any large vessels of the uterus; (2) the identification and exposure of the tongue-like fold of peritoneum is easy because it is at all times under direct visual control; (3) more room can be obtained by this technique than by any variety of extraperitoneal cesarean section so that the delivery of a baby of more than average size should be of no great concern to the operator; (4) that the technique herein described, if followed carefully, can be performed with ease, safety, and without the expenditure of too much time. The results, I believe, will be highly satisfactory, and it is my sincere hope that further experience in the hands of other obstetricians will prove me to be correct.

### Technique

A midline incision is made in the abdominal wall extending from a point one inch below the umbilicus to the pubes. The recti muscles are dissected from their sheaths and retracted laterally (Fig. 1). The transversalis fascia and the peritoneum are incised vertically for about one or one and one-half inches; the lower end of this incision reaches a point about one-half inch above the parieto-vesico-peritoneal reflection. The peritoneal edges are grasped by forceps applied laterally (Fig. 2). The wound is spread out in a transverse fashion, as shown in Fig. 3. This raises the bladder somewhat and brings it more clearly into view. The peritoneum is then separated from the bladder, starting in the midline, proceeding toward the left bladder angle, and finally, the right bladder angle is freed. This is done by sharp dissection in the midline and over the fundus of the bladder, where the peritoneum is usually very adherent. This part of the dissection is carried out under direct vision and it is made easy by one or two fingers within the abdomen (Fig. 4). These fingers lift up and put the peritoneum on a stretch. Once the fundus of the bladder has been freed of its peritoneum, it will be found that the peritoneum will now strip off the rest of the bladder with ease by using a gauze sponge until the vesico-uterine reflection of peritoneum is reached. This tongue-like fold of peritoneum which looks like a hernial sac must not be injured. This is, as Waters justly states, "the most important part of the entire operation." If desired, one may proceed, as in the Waters' operation, to denude the bladder of its fascia, which remains

A large femoral hernia was noted extending from the right inguinal area to just above the knee. At the most dependent portion of the hernial sac was an ulcer 2 cm. in diameter, and from this point there was a constant discharge of a clear yellow-tinged fluid. The extremities were negative; there was no ankle edema.

The patient was immediately sent to City Hospital with a tentative diagnosis of Meigs's syndrome and femoral hernia. At the hospital, the clinical work-up showed the following:

*Blood Count:*

Hemoglobin	—	86% or 14.6 Gm.
R.B.C.	—	4.2 million
W.B.C.	—	12,150
Differential	—	normal
Type	—	0

Blood sedimentation time—1 hour plus

*Urine:*

Specific gravity	—	1.025
Albumin	—	1 plus
Sugar	—	negative
Microscopic	—	occasional hyaline casts

*Blood Chemistry:*

Sugar	—	73 mg. %
N.P.N.	—	35 mg. %
Serum albumin	—	4.13
Serum globulin	—	2.16
Total blood protein	—	7.7 mg. %
Wassermann	—	negative

*Chest X-ray:* Marked elevation of both diaphragms, especially the right and pleural effusion in the right lower chest which extends into the interlobar fissures.

The possibility of a vesicoinguinal fistula was considered. This was ruled out when injection of methylene blue into the bladder failed to color the discharge from the hernial sac.

At City Hospital the patient was seen by all members of the visiting staff, one or two of whom urged delay, believing that operation could only result in a fatality. It was suggested that the pathology would soon be revealed at autopsy. This conclusion was in spite of the fact that Meigs's syndrome was considered by all as a possible diagnosis. It is apparent, therefore, that the importance of Meigs's conclusion in his original paper, namely, that "the curability of certain seemingly hopeless conditions is emphasized"<sup>8</sup> has been overlooked by many.

On Sept. 18, 1944, the patient was transferred to a private institution. That evening, 2,500 c.c. of clear yellow fluid was removed from her right chest in order to increase the aeration capacity of her lungs. No work-up was done, since all laboratory data were available from City Hospital. On September 19, a laparotomy was performed. The anesthesia used was intercostal block plus cyclopropane for the few minutes during which the tumor was being lifted from the abdomen. The abdomen was opened with a right paramedian incision and 500 to 750 c.c. of clear straw-colored fluid was noted. A large, smooth, almost round tumor of the right ovary, about 27 cm. in diameter, was found. The uterus itself was small and atrophic; the left tube and ovary were normal; the right tube was considerably elongated and thickened, but otherwise normal. The abdominal cavity was remarkably free of small and large bowel, since most of the intestines were in the hernial sac. A rapid right salpingo-oophorectomy was done and the abdomen closed in layers without drainage. During the operation a transfusion of 500 c.c. of blood was given, followed by 1,000 c.c. of 5 per cent glucose in normal saline intravenously.

CASES OF MEIGS'S SYNDROME

SITE OF TUMOR AND SIZE	LOCATION OF HYDROTHORAX	THORACENTESIS	ABDOMINAL PARACENTESIS	FLUID AT OPERATION
Bilateral; L—17 × 15 × 9 cm. R—small orange	Left	1	1	Not given
Left; size of grapefruit	Bilateral	0	0	9 qts. clear amber-colored fluid
Right; 1,300 Gm. 17 × 14 × 11 cm.	Right	12	0	1,500 c.c. straw-colored fluid
Bilateral; R—13 × 9 × 9.5 cm. L—3.5 × 4 × 3 cm.	Right	More than 9 times	0	200 to 300 c.c. clear yellowish fluid
Right; 20 cm.	Right	1	0	Not given
Right;* 15 × 23 × 23 cm.	Bilateral	6	0	Not given
Left; medium-sized melon	Right	0	2	Abundant serosanguineous
?	Right	Repeated	Repeated	Not given
Left; 12 × 7 × 7 cm.	Right	0	0	1 gallon
Right; 20 × 15 × 10 cm.	Bilateral	4	0	Not given
Left; 17 × 15 × 10 cm.	Right	3	1	Considerable amount
Left; 5 × 6 in.	Right	2	0	Some clear straw-colored fluid
Right; 20 × 20 × 15 cm.	Right	1	0	Considerable amount of clear yellowish ascitic fluid
Left; 1,370 Gm.	Bilateral	4	0	Considerable amount of ascitic fluid
Left; 8 in.	Right	1	0	Small quantity
Right; 7 × 6 in.	Right	Repeated	1, no fluid	Less than 1 pint
Right; 27 × 20 × 20 cm. 5,200 Gm.	Bilateral	1	0	750 c.c. straw-colored fluid

### Conclusion

1. A case is reported in which a solid ovarian tumor weighing 5,200 Gm., associated with ascites and hydrothorax, has been removed from a patient in an apparently hopeless condition.
2. Patients with Meigs's syndrome are in all probability being overlooked.
3. Attention is called to a possible minor postoperative complication which will surely prove distressing to the patient, if not to the physician.
4. The importance of giving every patient who presents the triad of pelvic tumor, ascites, and hydrothorax the benefit of operative exploration, no matter how hopeless her condition, is emphasized.
5. The term "Meigs's syndrome" should be reserved for those cases which present a solid ovarian tumor associated with ascites and hydrothorax.

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*Pathology.*—*Gross:* The specimen consisted of an encapsulated, somewhat irregular mass 26 by 23 by 17 cm. in size. The consistency was hard, and the cut surface showed white interlacing bundles of fibers in a grayish stroma. In one area, toward the periphery, a few small cysts, up to pea-size in diameter, were seen. Prominent dilated vessels were noted in the capsule, and small subcapsular hemorrhagic areas were present. Attached at one area was a tube 7 cm. in length and 0.3 cm. in diameter which was patent.

*Microscopic:* Sections showed small stellate cells with small spindle-shaped nuclei. They were arranged partly in parallel bundles, partly showed an interlacing pattern. Intercellular substance was scarce. The cells were uniform in appearance and did not show any evidence of hyperactivity.

*Diagnosis:* Fibroma of the ovary.

The postoperative course was almost incredibly uneventful, with the exception of the polyuria and resultant overdistention of the bladder discussed below. The temperature on the first postoperative day went to 102° F. at one reading, and thereafter was never above 100° F. On the fifth postoperative day, all signs of hydrothorax had completely disappeared. The patient was discharged from the hospital on her twelfth postoperative day, weighing 87 pounds. Just prior to discharge, a chest fluoroscopy revealed no evidence of hydrothorax.

An interesting and unanticipated minor complication followed excision of the tumor. The patient voided spontaneously shortly after operation and passed an average of 1,500 c.c. of urine a day which seemed more than adequate, considering that she was not receiving an excessive amount of fluid by mouth and had been given only one intravenous of 1,000 c.c. of 5 per cent glucose in normal saline postoperatively. By the third day, the patient was voiding involuntarily in bed and complaining bitterly of suprapubic pain. I catheterized her and obtained 1,500 c.c. of urine notwithstanding the fact that during the previous twenty-four hours she had passed an equal amount. The resorption of the pleural exudate following operation was so rapid that the patient developed an overdistended bladder. This conclusion is substantiated by the fact that a careful physical examination of the chest on the fifth postoperative day revealed no signs of pleural effusion.

*Follow-up.*—After three weeks of convalescence in the country, the patient was again seen in my office on Oct. 5, 1944. She stated that she felt better than she had in years. She weighed 103 pounds; the scar was firm and, amazingly enough, the hernia had shrunk to about the size of an apple. The fistula had, of course, healed, and the skin covering the hernial sac had the wrinkled appearance of a scrotum. Most of the mass was made up of skin rather than abdominal contents. Two months later she weighed 112 pounds, the hernia had almost completely disappeared, but there was still a strong impulse on cough below Poupart's ligament in an area about 3 cm. in diameter. The blood pressure continued to be 190/100, but her general condition was otherwise excellent, and at this time she returned to work. On March 22, 1945, she weighed 123 pounds; the hernial sac had further shrunk, and she was told to limit caloric intake, as further weight gain was deemed inadvisable. She was last seen on April 4, 1946, and was in good health except for her hypertension.

### Discussion

This case is a classic example of Meigs's thesis, that one must operate when operation is the sole hope. The patient was dying because of ascites and the constant loss of protein-bearing fluid, plus her actual physical inability to take in an adequate amount of food. This, in turn, was due to the limitation of space in her abdominal cavity because of the tumor itself.

tained papillary carcinoma tissues arranged on branching stalks of vascular fibrous stroma with infiltrations of lymphocytes. The carcinoma cells on these stalks had large vesicular nuclei and granular cytoplasm. Many were in mitosis. In some regions they formed masses of cells in which there were a few crevices and with small cores of fibrous tissue; in other regions their arrangement was more distinctly papillary on branched villous projections resembling the Fallopian tube. There was also some fibrous and smooth muscle tissue from the wall of the tube, having along the edge a few fibrous villi lined by columnar epithelium and continuous with an epithelium several layers deep with irregular projections. The histologic diagnosis was primary carcinoma of the Fallopian tube.



Fig. 1.—Gross specimen. The three arrows indicate the periphery of the left ovary.

The postoperative course of the patient was uneventful, and she was discharged on the fourteenth postoperative day. Deep pelvic x-ray therapy consisting of a total of 4,000 roentgen units was started before the patient was dismissed. In Sept. 1946, four months after surgery, there was no palpable evidence of carcinoma.

The other six cases are briefly described below.

CASE 2.—N. T., a 59-year-old para i, gravida ii, whose last menstrual period had been eleven years previously, entered St. Luke's Hospital July 22, 1924, because of left lower quadrant pain for six days. She had had chills and fever prior to admission. At operation the uterus was normal. The left Fallopian tube was 12 cm. long and within the lumen of the dilated distal end there was a firm mass 6 cm. in diameter consisting of yellow granular tissue. Microscopically, the lining of the Fallopian tube was composed of papillae with delicate fibrous stalks on which were several layers of proliferating epithelium, the outer layers columnar. The papillary masses infiltrated the wall of the tube. The histologic diagnosis was papillary carcinoma of the Fallopian tube.

CASE 3.—E. N., a 40-year-old nulligravida, with normal menses, entered St. Luke's Hospital Oct. 5, 1926, because of acute abdominal pain of twelve

## PRIMARY CARCINOMA OF THE FALLOPIAN TUBE\*

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THERE have been about 450 cases of primary carcinoma of the Fallopian tube reported in the literature up to the present time. A few of these have not been acceptable so that, at best, it is difficult to obtain an accurate count of this relatively rare disease. The accepted incidence is between 0.2 and 0.5 per cent of gynecologic malignancies. The age group is mainly in the fifth decade. Clinically the diagnosis is seldom made preoperatively and not always at the time of surgery. Most frequently it is made on microscopic examination of the tissue; over 95 per cent of the lesions are accounted for in this manner.

Seven cases of primary carcinoma of the Fallopian tube have occurred at St. Luke's Hospital since 1924. In one of these a tentative preoperative diagnosis of carcinoma of the tube was made. The latter case is described in detail, and the other six are briefly discussed.

### Case Reports

CASE 1.—The patient, aged 56 years, white, para iv, gravida v, entered St. Luke's Hospital May 20, 1946. About one month before admission she noted a yellowish to brown viscid discharge from the vagina sufficient in amount to require her to wear a napkin. Two weeks following this, the discharge was blood-tinged for one day. At this time she developed a dull aching pain in the lower back and left lower abdomen. The patient had had a normal menstrual life; her last menses had been at the age of 53 years. She had a right mastectomy for a tumor the nature of which is not known. Family history for carcinoma was negative. The vaginal examination revealed a normal cervix and uterus. The right adnexa was considered normal on palpation. There was a soft, elongated, orange-sized, adherent mass in the left adnexa, which was thought to be the Fallopian tube. The left ovary was not palpable as such. A diagnosis was made of primary carcinoma of the left Fallopian tube. The patient was operated upon May 21, 1946.

At operation there was an estimated 250 c.c. of a chocolate colored fluid free in the abdominal cavity. There was an elongated, soft, red-blue adherent mass 6 cm. in diameter involving the left tube. The normal left ovary was loosely adherent to the mass. There was a right adherent tubo-ovarian inflammatory mass. There were several small fibromyomas in the wall of the uterus; the cervix was normal. A complete hysterectomy and wide removal of the adnexae was done. The left tube when opened revealed a papillary carcinoma tissue confined within the tubal wall. There was no demonstrable extension in the broad ligament, on the peritoneum, in the preaortic or the hypogastric lymph nodes. The right tube was opened and contained no evidence of carcinoma. The surgical diagnosis was primary carcinoma of the left Fallopian tube.

The essentials of the pathologic description were as follows: the dilated left tube was 10 cm. long and about 3 cm. in diameter; in the lumen there was a large amount of soft gray friable polypoid tissue that extended for a length of 5 centimeters. Both ovaries were normal. Microscopically, the left tube con-

\*Presented before the Chicago Gynecological Society, Oct. 18, 1946.

had lost 22 pounds in six months. A right salpingectomy had been done for adhesions at another institution fifteen years previously. At operation the uterus was normal. The enlarged left tube enclosed a cystic tumor mass 9 by 7 centimeters. There was a bloody fluid in the cystic mass, and the wall was lined by red granular trabeculae. The wall ranged to 2 cm. in thickness. Microscopic sections revealed villous structures like those of the Fallopian tube. The villi were on narrow fibrous stalks and covered by a many layered columnar epithelium. In some places the epithelium had ingrown the wall of the cyst and formed tubular structures. In other places there were aggregates of epithelial cells without differentiation forming papillary tubular structures. The histologic diagnosis was carcinoma of the Fallopian tube. This patient died three years later as a result of metastases.

CASE 5.—A 49-year-old para ii, with normal menses, entered St. Luke's Hospital March 24, 1935, because of a feeling of pressure in the lower abdomen for two months. She also noted that her abdomen had become larger in the three weeks prior to admission. She had lost 16 pounds in two months. At operation there was a blood-tinged fluid in the abdominal cavity. The peritoneum and the uterus were studded with small nodules. The right Fallopian tube was 1 cm. in diameter at the uterine end and increased up to 4 cm. in diameter, distally, where it formed a stalk of a large cauliflower mass 16 by 12 by 6 centimeters. There was a similar mass 14 by 10 by 9 cm. alongside. Sections of the masses were gray-yellow tissue with scalloped edges. The right tube, when opened, revealed a similar gray-yellow tissue within the lumen. Microscopic sections revealed scanty fibrous stalks covered by palisades of columnar epithelium. There were also columns of these cells apparently fused into aggregates or mosaics of cells. Other tissues had a papillary arrangement. The cells were medium in size, with vesicular nuclei, and a moderate amount of cytoplasm. Many were in mitosis. The histologic diagnosis was papillary carcinoma of the Fallopian tube.

CASE 6.—S. H., a 60-year-old nulligravida, whose last menstrual period had been five years previously, entered St. Luke's Hospital May 11, 1936, because of a hard swelling of the lower abdomen associated with a pulling aching sensation for two months. At operation the uterus was normal. The markedly thickened right tube was 12 cm. long. A cystic mass 10 by 15 cm. originated from within the dilated end of the tube. The cyst contained 400 c.c. of a dark brown fluid. The wall in places was 1 cm. thick and was lined by a gray granular tissue. The microscopic sections revealed a dense fibroblastic stroma ingrown by masses of epithelium arranged in mosaics and tubules. Along the lining of the tube were papillary folds with edematous fibrous stalks lined by a several layered epithelium. The invasion of the tissues by the ingrown masses of epithelium extended to just under the peritoneum of the tube. A subperitoneal lymph node included was composed of masses of metastatic carcinoma cells in mosaics. The histologic diagnosis was papillary carcinoma of the Fallopian tube with local lymph node metastasis.

CASE 7.—L. O., a 48-year-old single woman, whose last menstrual period had been six years previously, entered St. Luke's Hospital July 11, 1939, because of pain in the left lower abdomen of six months' duration. At operation the uterus was normal. The left Fallopian tube resembled a large pyosalpinx 20 cm. long and 8 cm. in diameter. Within the lumen at the distal end there was a mass of necrotic yellow tissue. The wall of the tube, in places, was 1.5 cm. thick. Both ovaries and the right tube were normal. Microscopic sections revealed a fibroblastic stroma extensively ingrown by large and small irregular



hours' duration. The abdomen was distended. At operation the left tube was markedly dilated, club-shaped, 21 cm. long, and extruding through the end there was a firm gray-yellow mass 3 by 3 by 2 centimeters. The dilated, firm right tube was 12 cm. long and within the lumen, in the distal portion, there was a similar gray-yellow tissue. There were numerous small nodules of this tissue over the surfaces of the peritoneum and omentum. The uterus was not



Fig. 2.—Microphotograph of vascular fibrous villous with many layered epithelium of carcinoma cells. ( $\times 198$ .)

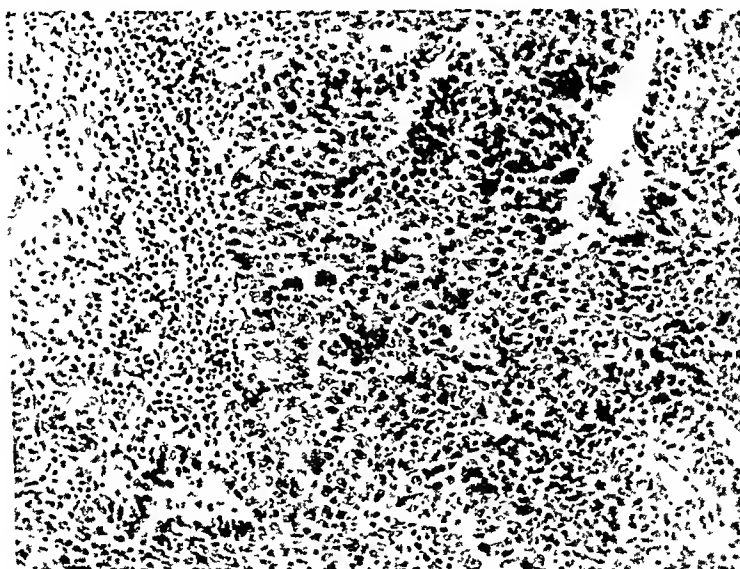


Fig. 3.—Microphotograph showing the solid masses of carcinoma cells. ( $\times 198$ .)

significant. The ovaries were not identified. The microscopic sections revealed infiltrating masses of epithelium arranged in papillary structures, but in some places tubular. The histologic diagnosis was bilateral carcinoma of the Fallopian tubes.

CASE 4.—F. H., a 58-year-old, para 0, gravida iii, whose last menstrual period had been five years previously, entered St. Luke's Hospital June 13, 1928, because of a vaginal discharge and slight bleeding of ten months' duration. She had had left lower abdominal tenderness for ten months, and she

## PREGNANCY COMPLICATED BY COARCTATION OF THE AORTA

EDMUND R. NOVAK, M.D., BALTIMORE, MD.

COARCTATION of the aorta is a rare complication of pregnancy, Mendelson, in 1941 having been able to collect only 29 cases, including three of his own. The latter three cases were seen among approximately 31,000 obstetric patients at the New York Lying-In Hospital. In Mendelson's series, the patients had an average of about three previous pregnancies each. Of the 25 women, five died during pregnancy or shortly after delivery, two from rupture of the aorta, one of cardiac failure, one of cerebral accident, and one of bacterial endocarditis. Moreover, 10 patients who survived delivery suffered a definite aggravation of cardiac symptoms as the result of the pregnancy.

In view of these findings, it is not surprising that Mendelson regards coarctation of the aorta as an exceedingly grave complication of gestation, and states firmly that any woman with this condition who comes under observation in the early months of gestation should have the pregnancy terminated. If gestation is more advanced, close observation followed by cesarean section and sterilization is his recommendation. Other observers, notably Hamilton, Walker, Eastman, and others, believe that certain of these patients can, under close supervision, be carried to full term and delivered normally. Very few persons with coarctation of the aorta live beyond 40 years, over 75 per cent of them dying of cardiovascular causes. From a theoretical viewpoint, it would certainly appear that in pregnancy the increased blood volume, cardiac output, and generally greater load would impose on these patients a severe, possibly unjustifiable strain.

In view of the fact that coarctation of the aorta is a most uncommon complication of pregnancy, and at the same time is one in which the question of therapeutic abortion will frequently arise, it would seem desirable that as many cases of this condition as possible be reported in order that the prognosis of gravidas with coarctation may be more intelligently evaluated, and the management of this condition put on a well authenticated basis. To this end the following case is reported.

### Case Report

This 21-year-old white female, para 0 of Venezuelan descent, presented herself at the U. S. Naval Dispensary, Annapolis, Maryland, on January 9, 1946. Her periods had always been normal. Menses had begun at 12 years of age, occurred every thirty-one days, and were of three to four days' duration. Her last menstrual period was Oct. 19, 1945. She had always been in excellent subjective health. She had had the usual childhood diseases. While at high school in 1940 a mild hypertension was noted, although she had always been symptom-free. In subsequent years, a checkup as regards the hypertension revealed an x-ray picture typical of coarctation. Pyclograms revealed only one functioning kidney, and that there was only one kidney was confirmed in 1943 during an exploratory laparotomy, at which time her appendix was removed.

Examination of the patient revealed that she was approximately fourteen weeks pregnant, and arrangements were made to have her admitted to the hospital for a thorough study, as well as a possible interruption of the pregnancy, should the study seem to indicate this.

masses of epithelium that were arranged in mosaics. The individual cells were moderately large and had large vesicular nuclei. In some places there were tubules, and in other places there were blunt papilli with broad stalks covered by epithelium in many layers. The histologic diagnosis was carcinoma of the Fallopian tube.

### Discussion

In our own detailed report, a preoperative diagnosis of carcinoma of the tube was made, although an ovarian tumor could not be ruled out. The history of postmenopausal serosanguineous discharge combined with the pelvic findings of an apparently normal uterus and cervix and a soft elongated mass in the adnexa were suggestive of tubal rather than ovarian pathology.

From our experience at St. Luke's Hospital and from a review of the literature, we feel that a positive diagnosis of primary carcinoma of the Fallopian tube cannot be made except on rare occasions, but it may be strongly suspected from the symptomatology and the pelvic findings as described above. It is difficult to rule out ovarian pathology which is more common than tubal carcinoma. At times it may be impossible to determine, microscopically, whether the primary origin of the carcinoma is in the ovary or in the tube.

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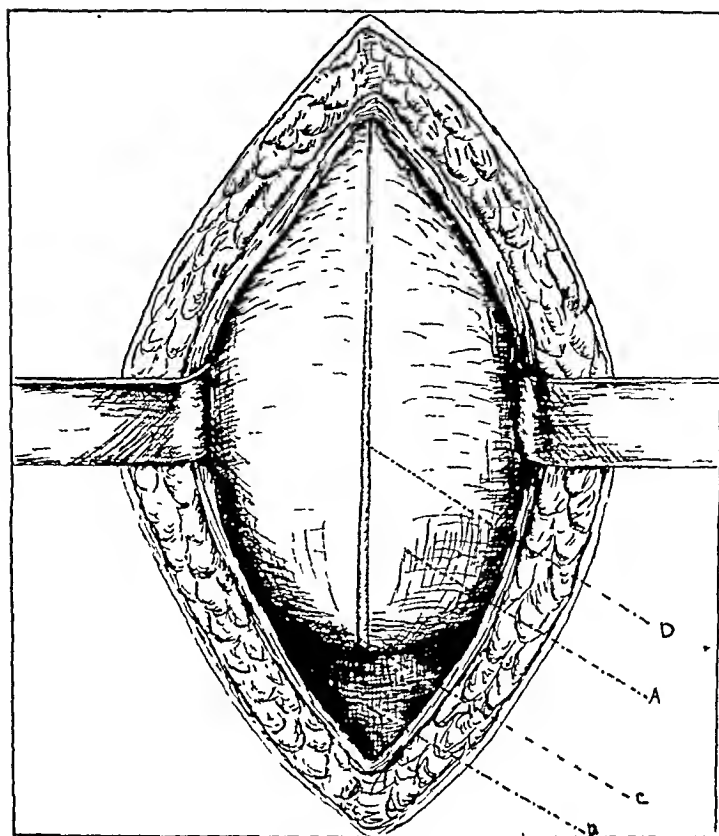


Fig. 1.—A—Transversalis fascia; B—bladder; C—parieto-vesico-peritoneal reflection; D—median umbilical ligament.

The recti muscles are retracted laterally, bringing to view the parietal peritoneum, fascia transversalis, and bladder. The urachus, shining in the midline, is seen to end at the apex of the bladder.

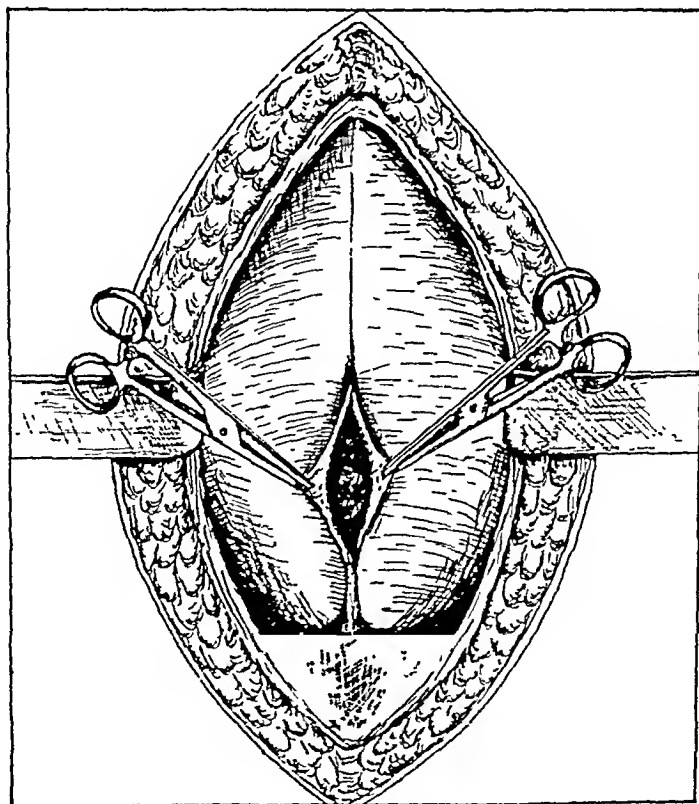


Fig. 2.—Incision of transversalis fascia and peritoneum. The edges are grasped with forceps.

A fuller examination at the hospital revealed the following positive and pertinent factors. The patient was a well-developed and well-nourished individual, with no signs of dyspnea or cyanosis. The eye grounds were normal. Blood pressure in both arms was 155/80; in the right leg it was 115/60, and in the left, 120/65. The chest was clear. The heart was of normal size and shape, the sounds were of good quality, and there was regular rhythm. There was a soft substernal systolic murmur, not transmitted. There was no external evidence of an increased collateral circulation anywhere over the trunk or back. Pelvis was adequate and of a normal gynecoid type.

Various studies were made on the patient during her hospitalization. The Kahn was negative and blood counts and blood chemistry were normal. There was no albuminuria, nor was there ever any throughout the course of her pregnancy. Intravenous pyelograms showed "normal psoas and left renal shadows. Five minutes after injection of dye there was excretion on the left side, continued at 15 and 30 minutes. The left calices, pelvis, and ureter were normal. The right kidney did not visualize." The left kidney seemed to have fairly good function, the P. S. P. being 55 per cent for two hours; 35 per cent in one-half hour; 15 per cent in one hour; 5 per cent in two hours. In the dilution concentration test the urine varied from 1.003 to 1.025.

A chest plate confirmed the diagnosis of coarctation. There was definite notching of the inferior borders of the fifth to ninth ribs, consistent with the condition. The aortic arch was hypoplastic, and the cardiac silhouette within normal limits. Electrocardiogram revealed "slight left axis deviation. All complexes normal save flat T wave in lead 3." Our cardiologist interpreted the cardiogram as showing "possible myocardial damage."

It was felt that this patient could go through to term, but not without some risk, and this risk was explained to her. She was extremely anxious for the baby, and was more than willing to take the hazard which was pointed out to her. Accordingly, she was carried along watchfully, with weekly visits to the dispensary.

The course was benign for the next two months. Her pressure did not rise, the urine was negative, and there were no complaints. In March she developed an arrhythmia which persisted until term, but several electrocardiogram examinations showed only premature ventricular contractions, and little significance was attached to them.

On June 24, approximately one month before term, the pressure began to increase slowly to 170-185/100-110. The customary regime of phenobarbital, rest, salt, and fluid restriction, dietary measures, etc. was begun, and there was no further increase in pressure. It was felt that not too large a baby was desirable, and accordingly, on July 12, medical induction was attempted, but failed.

On July 22, the patient was found to have a pressure of 200/120, and she was admitted to the hospital at once. In addition she had an extremely bad severe upper respiratory infection. Because of this, surgical induction was postponed, though the membranes could have been ruptured easily. She was sedated, and the upper respiratory infection treated, preparatory to induction. Her pressure came down and remained at about 160-170/100 as the upper respiratory infection gradually improved and her temperature returned to normal. On her third day in the hospital she went into spontaneous labor, and as soon as the pains became established she was given nembutal and paraldehyde in adequate amounts. Amnesia was excellent, and the labor lasted less than ten hours.

During labor, the pressure ran as high as 230/130 in the arms, and 140/100 in the legs, but there were no sequelae. Delivery was by elective low forceps, with right mediolateral episiotomy under gas, oxygen, ether anesthesia. A normal 6 pound, 9 ounce male baby was delivered uneventfully. The post-partum course was entirely smooth and asymptomatic, marked by a gradual lowering of the pressure to 150/90, the level at which it had been noted in her first dispensary visit. She was discharged from the hospital on her ninth post-partum day, entirely symptom-free.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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### Gynecology

Paris, 1946: The Disturbances of Ovulation, Proceedings of the 10th French Congress of Gynecology, May, 27-29, 1946.

The proceedings of the Tenth French Congress of Gynecology is entitled "Disturbances of Ovulation." This meeting was held at Lyon, May 27 to 29, 1946, and the seven papers presented at that time are contained in this 164-page proceedings.

G. Dubreuil Bordeaux discusses the histophysiologic and morphologic aspects of the ovary in terms of recent investigative work. This first paper, of French Congress, reviews in considerable detail the microanatomy of the ovary describing in order the evolutionary, degenerative, and involution cytohistologic changes. Each of these representative findings are discussed separately in the categories of the control zone, the undulatory zone, and the ovarian epithelia. He concludes with a description of the various types of ovaries, viz: the embryonic, fetal, infantile, prepubertal, and pubertal types. He distinguishes the ovary of the early adult sex activity from that of late sex activity; the changes which are found in the premenopausal to menopausal period, and the postmenopausal ovary to the fully senile organ.

R. Moricard, of the Broca Hospital's Gynecology Clinic and Postgraduate School's Endocrine Laboratory in Paris, considers "the mechanisms of ovulation and the standardization of gonadotropins." He divides his discussion into three main parts: (1) a historical review of the physiology of ovulation, (2) the quantitative standardization of endocrines in rodents as based upon the 1939 International Standards, and (3) the methods for the dosage determination of gonadotropins essential to induce ovulation in the primates and woman. The author admits this third problem is far from resolution, although it is his opinion that experimental work seems to indicate that the injection of serum gonadotropins is inclined to produce greater regularity of ovulation in woman than the use of chorionic pituitary gonadotropins.

Raoul Palmer, of Broca Hospital, Paris, presented an interesting third paper entitled "Tests for Ovulation in Woman." In the category of true tests of ovulation the author considers the recovery of ova or concepti at time of laparotomy, impregnation following single exposure, and conception following application of the Ogino-Knaus method of calculating the time of ovulation. The author reviews many of the usual methods used to determine ovulation, including: clinical signs; vaginal biopsies and smears; cervical tests concerned with viscosity changes of the mucus, its pH and refractive index; endometrial biopsy; the uterine muscular tests of Knaus, Varangot, and his own; the hormonal tests concerned with total estrogens, fractional estrogens, urinary pregnandiol excretion, and blood levels, along with the chemical tests of Takata and Domoto and Samuels. He adds a full review of potentiometric methods and basal body temperature. Palmer concludes by listing the criteria of ovulation evidence in order of descending value as a diagnostic method: (1) intermenstrual crisis, (2) intermenstrual spotting, (3) cervical mucus changes in viscosity, (4) basal body temperature, (5) glycogenic activity in secretory endometrium, (6) the vaginal smear, (7) the bio-assays of urinary steroids, and (8) the potentiometric study.

M. E. Guéissaz, of Neuchâtel, reports on the topic of: The Intermenstrual Crisis. This author concludes by redescribing the typical syndrome associated with rupture of the follicle. He states that the symptomatology varies because the co-existent utero-adnexal conditions vary, and that other known and accepted criteria of ovulation show a close correlation to this intermenstrual crisis syndrome.

Wm. J. A. Schockaert and J. Ferin, of Louvain, next considered the role of disturbances of ovulation in gynecologic pathology. They define several new terms not usually considered in this country: (1) eu-ovulation, indicating a normal rupture of the follicle, (2) dysovulation, connoting follicular rupture without extrusion of the ovum or with the expulsion of an immature ovum, (3) paraovulation, denoting ovulation occurring at other than anticipated times as in the course of the folliculino-progestin phase. These authors emphasize the role of anovulation to gynecologic pathology as seen in menstrual disorders, and conclude that our knowledge and evidence indicating the etiologic factors of anovulation are "very fragmentary and often contradictory."

M. J. Figarella, of Marseille, the second from the last speaker at the Tenth French Congress on Gynecology, considered "the hemorrhages of follicular origin." He divided his subject into four main parts following an historical review; (1) the clinical problem, in that more than half of these cases occur in adolescent girls and that more than four-fifths of all these cases occur in women before the age of 30 years; (2) the diagnostic problem which he considered not difficult, and proceeded to list four cardinal and four secondary diagnostic signs; (3) the biologic problem, concerned principally with evaluation of pathogenetic hypotheses; and (4) the therapeutic problem. Therapy was the preventive and curative methods. for the former no definite suggestion is made. The cure is obtained practically always by surgery which should be extremely conservative—usually suture of the bleeding point with or without enucleation and partial resection.

M. G. Cotte, of Lyon, gave the final paper. Its title was "The Treatment of the Disturbances of Ovulation." Under medical therapy the author mentioned the use of yohimbine and prostigmin, but he concludes neither exerted direct action upon the ovulation process. He considered the various gonadotropins; touched briefly upon vitamins, A, B, C, D, and E, stressing the latter's value in infertility, and commenting he had obtained fair results in several cases exhibiting metrorrhagia, using intravenous vitamin C. Hydrotherapy, diathermy, and roentgen-ray therapy were considered, but the latter was not recommended. The author concludes with detailed evaluation of the usual and numerous surgical means used to control menstrual abnormalities.

This volume, "Disturbances of Ovulation" adds no new knowledge to our present understanding of this difficult subject. It is valuable in that it: (1) makes available excellent summarization of these problems, and (2) one can review most of the French literature on this topic in a single volume.

C. E. FOLSOME.

Vara, Paavo, and Pankamaa, Paavo: *A Clinical-Statistical Investigation of Ovarian Tumors Operated at the Helsinki University Clinic of Gynecology During the Years 1900-1944*, Acta obst. et gynec. Scandinav. 26: 1-78, Supplement 4, 1946.

The authors, Vara and Pankamaa, present an exhaustive and monographic summary, in eight chapters contained in this supplement, on a survey of ovarian tumors collected in Finland over a period of forty-four years. The survey material of 1,149 surgically treated tumors was collected from 33 years' experience at Helsinki University Gynecology Clinic and eleven years' experience at the Second Women's Clinic in the same school. Their excellent survey is entirely in English, and will provide an excellent comparative study data, particularly so since the authors completely reviewed the data in light of Miller's classification of tumors.

There were 37,811 total gynecologic cases treated in the above hospital, giving 1,149 ovarian tumors, an incidence of 3.04 per cent. There were 11,044 gynecologic operative cases, hence an incidence of 10.44 per cent of Finnish gynecic surgical cases exhibited ovarian tumors.

There were 48 (4.18 per cent) connective tissue tumors, of which nine cases (19 per cent) were malignant. There were 565 epithelial tumors (49.17 per cent) of which 221 cases (39.1 per cent) were malignant. Teratoid growths numbered 536, or 46.65 per cent, of which only 1.1 per cent were malignant. The benign tumors totaled 901 cases, 78.41 per cent; and the malignant 248, or 21.59 per cent.



The writers report that the most common ovarian tumor was the pseudomucinous cystoma, 322 cases, or 28.02 per cent. The second tumor in frequency rank was smooth-surfaced serous cystadenomas, 259 cases, or 22.54 per cent. Other ovarian tumors with a frequency greater than 10 per cent of the whole included dermoid cysts (208 cases, or 18.1 per cent) and primary carcinoma of the ovary (182 cases, or 15.8 per cent). The remaining types are listed in considerably detailed tables. Among the rarer ovarian tumors were four teratoma ovarii, 16 granulosa-cell tumors, four Brenner cell tumors, two myofibromas, one hypernephroma ovarii, and seventeen cases of pseudomyxoma peritonei, 148 per cent.

Most carcinomatous degeneration occurred in papillary cystadenomas, 37.9 per cent. The youngest case was aged 9 years, and the eldest, 79 years. Fifty per cent of the ovarian tumors were found in patients between the ages of 30 to 49 years, 25 per cent between 30 to 39 years, and 24.8 per cent between 40 to 49 years. The menarche average age was 15.46 years, which corresponds to average age of Finnish women. The authors' section on relation of ovarian tumors to fertility is excellently documented. They noted that the number of married cases, of their ovarian tumor series, reported as childless, was 122, or 15.66 per cent, which compares to 16.8 per cent of over-all childless marriages, after a duration of three years, as learned from the Finnish Central Statistical Bureau—indicating childlessness is not more frequent among ovarian tumor patients. The fertility index of patients who had given birth to children was 3.74 children average. It was not possible to demonstrate any different incidence of ovarian tumors in married or single patients. However, in certain tumor categories, some considerable differences were seen—in the primary carcinomas group the sterility incidence was 22.1 per cent, in secondary carcinomas 21 per cent, in dermoid cysts 15.9 per cent, in serous cystadenomas 14.9 per cent, in pseudomucinous cystomas 13.9 per cent, and in connective tissue tumors 8.1 per cent.

These usual ovarian tumors varied from fist to head size. Eighty-one per cent of the giant size tumors were pseudomucinous cystomas. In the largest tumor of the series 51 liters of pseudomucinous fluid were withdrawn. The bilateral frequency of all ovarian tumors was 14.62 per cent; present in 9.7 per cent of the benign tumors, and 32.7 per cent of the malignant growths. In the whole series 7.39 per cent of the tumors were intraligamentous. Torsion, as a complication was present in 16.27 per cent of all cases, and in increased frequency in cases under 20 years of age and over 60 years of age. As a result of torsion, hemorrhage was present in 15.5 per cent, necrosis in 15 per cent, perforation in 2.9 per cent, and blood-stained fluid in the abdominal cavity in 3.2 per cent of the cases. Infection or suppuration was present in 1.74 per cent of all cases.

The treatment in this large series of 1,149 cases of ovarian tumors was surgical and selective for the type of tumor. Tables list the various combinations of oophorectomy, salpingo-oophorectomy with or without hysterectomy and associated intestinal surgery. The over-all primary mortality was 3.74 per cent. The greatest mortality was in carcinoma ovarii cases (11.3 per cent) of which 18 per cent were secondary and 10.4 per cent primary, and the lowest mortality in the dermoid cyst cases, 0.5 per cent. The mortality among benign tumor patients was 2.1 per cent, and that among the malignant 11.2 per cent. It was highest in exploratory laparotomy cases (13.0 per cent), and lowest (2.2 per cent) in those cases having unilateral or bilateral oophorectomy.

Fatal complications included cardiovascular accidents, 1.71 per cent; peritonitis, 0.78 per cent; pneumonia, 0.61 per cent; ileus, 0.35 per cent, and meningitis and nephrosis each 0.09 per cent.

The authors submit no follow-up beyond the close of the first hospital discharge. Their data is superbly documented in 12 well-arranged statistical tables and one graph.

C. E. FOLSOME.

Teilmann, Gunnar: Arrhenoblastoma—Androblastoma. Homologous Ovarian and Testicular Tumors. II. Including the So-called "Luteomas" and "Adrenal Tumors" of the Ovary and the Interstitial Cell Tumors of the Testis, *Acta path. et Microbiol. Scandinav.* 23: 252-264, 1946.

The author, of Copenhagen, details a case of a feminizing testicular tumor occurring in a 53-year-old male. The tumor has been present for thirty years, and increased in growth

during the past two years. In the past three years there had been impotence and, during the last year, increasing gynecomastia. The latter finding subsided postoperatively.

Teilum suggests that for the case of survey and comparison, the homologous tumor series may be arranged in tabular order with similar but nonhomologous tumors belonging to the granulosa-cell group.

Under the category of homologous tumors of his androma series (arrhenoblastoma), he lists those found in the testis and the virilizing mesenchymomas of the ovary in two lists. The testis group include the androma (arrhenoblastoma), and the differentiated (tubular), intermediate and diffuse varieties. Variants of this group include the androma lipoides, of the tubular and diffuse types, and the "interstitial cell tumor." The virilizing ovarian group (mesenchyoma) includes the arrhenoma (arrhenoblastoma) and the differentiated (tubular), intermediate, and diffuse varieties. Variants of this group include arrhenoma lipoides of the tubular and diffuse types, tumors previously described as "adrenal tumors," "luteoma," "masculine ovoblastoma," and the "extraglandular" interstitial cell tumor.

Teilum compares the above two main groups with the granulosa-cell tumors, feminizing ovarian mesenchymomas as—granulosa-cell tumors of the differentiated, intermediate, and diffuse types and, as a variant of this group, the luteinized granulosa-cell tumor, thecoma.

The author, in a letter to Dr. Kosmak accompanying his reprints, stresses that he is of the opinion that his recommendations afford a more exact histogenetic classification comprising both ovarian and testicular tumors. His data is exceedingly well documented and illustrated with 14 photomicrographs and four tables. It does represent one of the most lucid classifications of these complex tumors that have come to the attention of oncologic students.

C. E. FOLSOME.

### Gynecologic Operations

Stamer, S.: Partial and Total Atresia of the Uterus After Exochleation, *Acta obst. et Gynec. Scandinav.* 26: 263-297, 1946.

Stamer reports his findings on 24 cases of uterine atresia of several types, following exochleation from the First Gynecological Division of Rigshospital, Copenhagen. The term atresia is defined in this article as partial or total, indicates closure of the uterine cavity or cervical canal. Exochleation is not defined, but strong inferences in the paper suggest it connotes almost complete epithelial denudation of the endometrium and/or cervical spindle epithelium.

The writer collects and details 37 cases from the literature and adds 24 cases from his institution. He finds the age of the patient not significant. In all 24 of the author's series the atresia was preceded by vigorous curettages of the puerperal uteri; and reported in non-puerperal uteri in only four of 37 cases in the literature series. There were six cases of total atresia, one from literature and five in the series studied by the author. Total atresia, with complete absence of endometrium, is practically symptom-free—save for amenorrhea.

Partial atresia is more often localized to the internal os; with symptoms of periodic pain and amenorrhea. The duration of the atresia seems to exert no harmful effect upon the endometrium, and normal menses are nearly always established after abolition of the atresia—in one case up to six years.

The usual therapy includes only dilatation procedures, although the author reviews many older surgical methods. In all the cases reported by the writer, every patient had experienced energetic curettage in other hospitals and came to Rigshospital because of symptoms of periodic pain and/or amenorrhea.

C. E. FOLSOME.

Davis, James E., and Cheek, David B.: Bleeding From the Cervix After Subtotal Hysterectomy, *J. A. M. A.* 131: 816, 1946.

The authors made a survey of the postmenopausal bleeding in their clinic covering a period of seven years. Eighty-seven cases of cervical stump bleeding were uncovered. Of this group 40 patients, or 46 per cent, were found to have a cervical cancer, and of these

40, there were 6, or 15 per cent, who had a benign-appearing cervix at the time they were first seen complaining of bleeding. The authors are of the opinion that every patient who has vaginal bleeding at any time after a subtotal hysterectomy deserves a biopsy of the cervix and a gentle curettage of the cervical canal. WM. BERMAN.

Young, Jr., John P., and Cole, Warren H.: Intraperitoneal Administration of Succinylsulfathiazole and Phthalylsulfathiazole, Arch. Surg. 53: 182, 1946.

The introduction of the oral use of succinylsulfathiazole and phthalylsulfathiazole as antibiotics for bacteria in the intestinal tract in colonic surgery by previous workers led the authors to investigate the absorbability of these drugs when they were introduced intraperitoneally. Experiments performed by them on dogs and humans revealed the fact that they were absorbed rapidly from the peritoneal cavity, although they were taken up only slightly when given by mouth. They also investigated the action of these drugs upon certain bacteria isolated from cases of peritonitis. They state that, although streptococci and other pyogenic bacteria are occasionally isolated, causative organisms in peritonitis, *Escheria coli*, is much commoner and, even when a mixed infection occurs, it is usually the predominant organism. Since both of these drugs are known to be extremely effective in reducing *Escheria coli* count of the stool, when given orally, the authors feel it is reasonable to suppose they would also be effective against the same organism in the peritoneum. They cite two cases in particular of their series of 51 cases where the drugs were given intraperitoneally, that substantiate this opinion. In each case, *Escheria coli* disappeared from the peritoneal cavity following implantation of phthalylsulfathiazole, although the other organisms were still present on the culture. In 28 patients of the series, succinylsulfathiazole was used, while on 23 cases phthalylsulfathiazole was injected intraperitoneally. The drug was either dusted in as a powder, or suspended in 20 to 30 c.c. of normal saline and poured into the peritoneal cavity. They advise that care should be taken lest the drugs get into the wound. Their presence in the wound will delay healing. The patients were watched closely postoperatively, but no toxic reactions were noted. E. C. HUGHES.

Tyrone, C. H., Collins, C. G., Weed, J. C., Zeigler, R. F., Jr., and Crawford, J. B.: Hysterectomy—A Study of 607 Cases, South. M. J. 39: 957, 1946.

Experience with hysterectomy is reviewed in a series of 607 cases of which there were 478 total abdominal, 100 vaginal, and 29 subtotal hysterectomies. The symptom most frequently seen was vaginal discharge. Pelvic pain and backache, hypermenorrhea, and polymenorrhea commonly associated with dysmenorrhea were observed in the abdominal group. It is interesting to note that 28 per cent of the group gave history of absolute sterility.

Pathologically, 44 per cent of the uteri showed leiomyoma. Endometriosis was present in 20 per cent, and malignancy in 8.2 per cent.

The morbidity rate based on a temperature of 100.4° F. on two consecutive days was 22.4 per cent for total hysterectomy group, 20.7 per cent for subtotal group, and 56 per cent for vaginal hysterectomies. WILLIAM BICKERS.

## Menstruation

Viggiano, F. A.: Dysmenorrhea in Industry. Treatment With a New Antispasmodic, Indust. Med. 15: 632-635, 1946.

Viggiano stresses the significance of dysmenorrhea as the most common cause of absenteeism and inefficiency among employed women, responsible for an average loss of two or more work days per month for each such employee.

The author became impressed with the results obtained from treatment of 112 dysmenorrheic patients treated at the Dispensary of the School of Aeronautics, June 1 to August 26, 1943, with pavatrine (beta-diethyl-aminoethyl fluorene-9-carboxylate hydrochloride), an ester

of an amino alcohol and an organic acid. He added recently to this first group a second group of 109 patients seen at the Harrisburg Shops' dispensary. The total group of 221 patients were given in all 243 courses, consisting in the main of a single dose of two tablets (0.25 Gm.) and an hour of bed rest.

The author concluded that pavatrine was safe and effective. Its use reduced absenteeism. In the whole series, 89.3 per cent of the treatments enabled the patients to return to work during the same day, and 76.6 per cent returned to work within one hour; full activity was possible in 51.5 per cent, and slight modification of activity in 25.1 per cent. The author compared results of pavatrine to another antispasmodic (tropic acid ester) in a third series of 128 cases, and obtained 76.6 per cent from the former and 64 per cent upon the latter. It is noteworthy that the degree of relief, however, was as follows: complete relief, 55.9 per cent; moderate relief, 19.1 per cent; slight or no relief in the remaining 25.0 per cent among the group of cases, aged 25 to 41 years.

It is unfortunate that the author failed to classify and correlate the degree of menstrual pain to therapy, and limited himself to the correlation of only the types of therapeutic relief. Furthermore, his article loses much significance in that he failed to include proper control series treated by placebo or suggestion.

C. E. FOLSOME.

**Grant, Alan:** Profuse or Irregular Menstrual Periods in Young Women: A Practical Programme of Treatment, *M. J. Australia* 113: 1946.

The author adopted the following standards before a case was designated as one of functional hemorrhage:

1. The hemoglobin value must be 80 per cent or less;
2. The menstrual periods must last longer than seven days;
3. The menstrual periods must occur at intervals of less than twenty-one days;
4. The diagnosis must be supported by diagnostic curettage. The curettage may be carried out in many cases with endometrial biopsy curette. In this series of cases, 66 per cent of the cases showed evidence of a hyperplastic endometrium, and a further 22 per cent showed abnormalities such as irregular ripening of the endometrium or hyposecretory changes or atrophy.

In many cases the curettage alone establishes a normal cycle. In cases where the patient is distressed by curettage, a 10-day course of cyclic therapy (stilbestrol and progesterone) is given. In cases where emergency treatment was necessary, the author used either curettage, large doses of estrogen, or intrauterine packing with gauze and drugs.

The author reviews the more standard methods of treatment at use during the present time.

WILLIAM BERMAN.

**Parella, Dominick:** Further Observations on Prostigmine in Delayed Menstruation and Pregnancy, *West. J. Surg.* 54: 397, 1946.

Vasodilatation in the endometrium induced by estrogen results from the liberation of acetylcholine. It was postulated that amenorrhea may be the result of a deficiency in acetylcholine. Prostigmine neutralizes the choline esterase permitting the available acetylcholine to function, thus inducing a hyperemia and menstruation.

Prostigmine was administered to 200 patients with amenorrhea. Uterine bleeding did not occur in amenorrhea due to pregnancy, endocrine disturbances, or the menopause. In all others except 6 cases, uterine bleeding occurred within seventy-two hours of completing the three-day course of injections.

**Fredrikson, Herbert:** The Role of the Thyroid in Certain Menstrual Disorders, *Acta obst. et gynec. Scandinav.* 26: 11-40, 1946.

Fredrikson, of Sundsvall, Sweden, reports in considerable detail his experience with nine selected cases of menstrual disorder either caused by or associated with a hypothyroid status.

All the cases cited exhibited hyper- or polymenorrhea, four of whom were biopsied and were revealed to have hyperplasia of the endometrium. Thyroid with or without iron constituted the therapy with good results in all nine cases. There are nine photomicrographs and one table in the article.

C. E. FOLSOME.

Pillay, A. P.: The Vitamin C Test for Ovulation, Indian M. Gaz. 75: 91, 1940; 75: 668, 1940; 77: 279, 1942.

More and more methods are being suggested for determining the day of ovulation in the menstrual cycles of women. Most of them seem to have some drawback, and others can be carried out only by doctors with special training. In this paper is described a test which can be carried out even by general practitioners.

The test used is a modification of the one used by Tillman to detect vitamin C deficiency in the system, and is based on the fact that vitamin C in excess of the requirements of the body is promptly excreted in the urine. For this any existing deficiency in the system must be corrected by administering vitamin C to the woman. The dose depends on vitamin C containing articles in the usual diet of the person, i.e., on her income group; 150 to 200 mg. appears to be the usual dose required.

One tablet of dichlor-phenol-indo-phenol (Roche) is dissolved in 50 c.c. of water. Five c.c. of the solution are pipetted into a beaker. Freshly voided urine is titrated quickly into this solution from a burette, and the quantity required to decolorize immediately the blue of this solution gives the quantity of vitamin C present in the sample of urine. Vitamin C reduces the dye dichlor-phenol-indo-phenol to its colorless leuco-derivative. The test should be completed within two minutes after the urine is passed. The result is chartered on graph paper.

It will be noticed that vitamin C excreted will be lowest on the day of ovulation, i.e., the quantity of urine required to decolorize the dye solution will be largest. This means that a marked upward curve will be noticed on that day. In anovulatory cycles, there will not be any pronounced curve, while in multiovular cycles, there will be more than one. The urine of men does not show any such variation in the excretion of vitamin C. In the graphs, the vertical figures indicate the quantity of urine in cubic centimeters required to decolorize 5 c.c. of the dye solution, and the horizontal figures the days of the menstrual cycle.

Though the test is carried out only from the day the menstrual flow stops, vitamin C is administered daily from the *first day* of the flow to correct vitamin C deficiency which is almost always present. The test has to be carried out daily in the first cycle as an exploratory measure, and in subsequent cycles it need be done only from the fifth to one or two days after the ovulation cure has been noticed.

It is advisable to carry out the test at the same hour every day to avoid upsets due to dietetic variations. The chief fallacy in the test is that if large quantities of water are drunk, the urine will be diluted and the curve will be upset. This should be forbidden. The test described may be varied by determining the actual quantity of vitamin C present in the urine. This is arrived at by dividing 10 by the quantity in c.c. of the urine required to decolorize 5 c.c. of the dye solution, which is equivalent to 0.1 mg. of vitamin C. In this modified test, the graph will show a reverse picture, i.e., the curve will be lowest on the day of ovulation. Other interesting findings were:

1. During the luteal phase of the menstrual cycle, the excretion of vitamin C in the urine is higher than during the follicular phase.

2. There is vast difference in the amount of vitamin C excreted in the urine when progesterone and estrin are administered, large quantities being excreted during progesterone administration and smaller quantities during estrin administration.

3. Vitamin C excretion in the urine is consistently high in cases of early pregnancy and in incomplete abortions.

A. P. PILLAY.

## Miscellaneous

Ensor, Charles R.: The Electrocardiogram of Rats on Vitamin E. Deficiency, *Am. J. Physiol.* 147: 477-480, 1946.

The author sought to evaluate the conflicting evidence in the literature concerned with the influence of vitamin E deficiency upon cardiac musculature. Five separate groups of patients were placed upon E-deficiency diets, including males and females in each series, and electrocardiograms were taken at intervals for a one-year period.

The author concluded that the electrocardiograms maintained for one year on an E-deficient diet was not different from electrocardiograms of normal rats, save possibly a slight exception—in one-third of one group there was a slight widening of the QRS complex.

C. E. FOLSOME.

Fordes, Thomas R.: The Origin of Freemartin, *Bull. Hist. Med.* 20: 461, 1946.

The author goes into considerable detail in discussing the origin of the word "freemartin." He states that the etiology of this word has never been fully established, but that it most certainly comes from nonclassical sources and did not have its origin in Latin or Greek. He, however, brings attention to the statement of John Hunter who first published on the phenomena of freemartin, and who stated that the Romans did have the female gender of the word "taura" to mean a bull which was nonfertile. The word "martin" apparently appears in writings from England and Scotland as early as 1220, and is apparently used to mean a cow or an ox or a spade heifer. There are several hypotheses regarding the origin of the word "free." The author suggests one possibility, namely that "free" may have had its origin from the Anglo-Saxon word "fearr" or "fear," meaning a bull or an ox. On this basis the author offers the hypothesis that freemartin may have signified an ox-like or bull-like cow just as the Roman word taura (feminine) may have indicated a female bull. "If freemartin and taura indeed had such meanings, then it is of course necessary to assume that at the times these terms came into use cattle raisers recognized that such animals possessed some essential sexual characteristics of both sexes." The author feels that this assumption seems not unwarranted.

L. M. HELLMAN.

## Newborn

Hill, J. M., and Haberman, Sol: Demonstration of Rh Antibodies in the Newborn and Further Evidence of the Pathogenesis of Erythroblastosis, *J. Lab. & Clin. Med.* 31: 1053-1066, 1946.

Hill and Haberman, of Dallas, offer additional evidence which tends to establish certain steps in the pathogenesis of erythroblastosis. They describe three varieties of Rh antibodies—agglutinating, blocking, and developing—found in both the newborn and the mother. The authors submit evidence that the Rh antibody acts as a hemolysin in vitro.

A careful analysis of 10 cases of erythroblastosis showed a relatively good correlation between the severity of the disease and antibody titer by the developing test. Therapy results indicated the advisability of immediate and adequate transfusion of Rh-negative blood in hemolytic disease of the newborn. The writers state breast feeding is contraindicated when Rh antibodies can be demonstrated in the maternal or fetal serum or adsorbed on fetal erythrocytes.

The authors conclude that the developing test as applied to the demonstration of adsorbed antibodies on fetal erythrocytes is a possible diagnostic test for erythroblastosis.

C. E. FOLSOME.

Barron, Donald H.: The Oxygen Pressure Gradient Between the Maternal and Fetal Blood in Pregnant Sheep, *Yale J. Biol. & Med.* 19: 23-27, 1946.

Barron, of Yale, observed that the oxygen pressure gradient across the placenta increases as gestation advances. The oxygen pressures in the fetal umbilical artery, umbilical

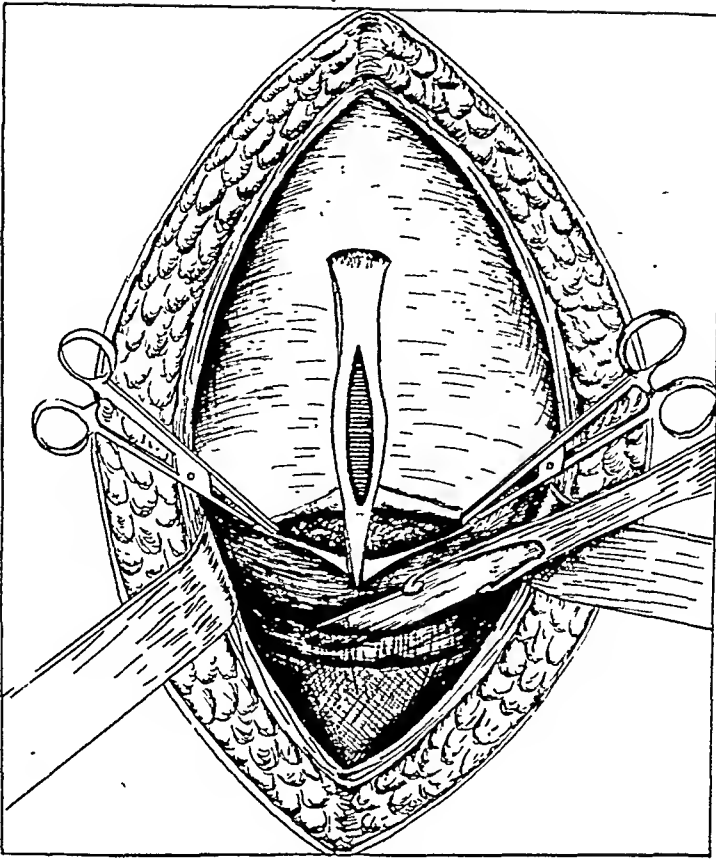


Fig. 3.—The wound is spread out in a transverse fashion. Thumb forceps can be used to elevate the lower edge of the wound. By sharp dissection with scalpel, the bladder is separated from its overlying peritoneum, starting in the midline, then proceeding to the left bladder angle and then to the right bladder angle.

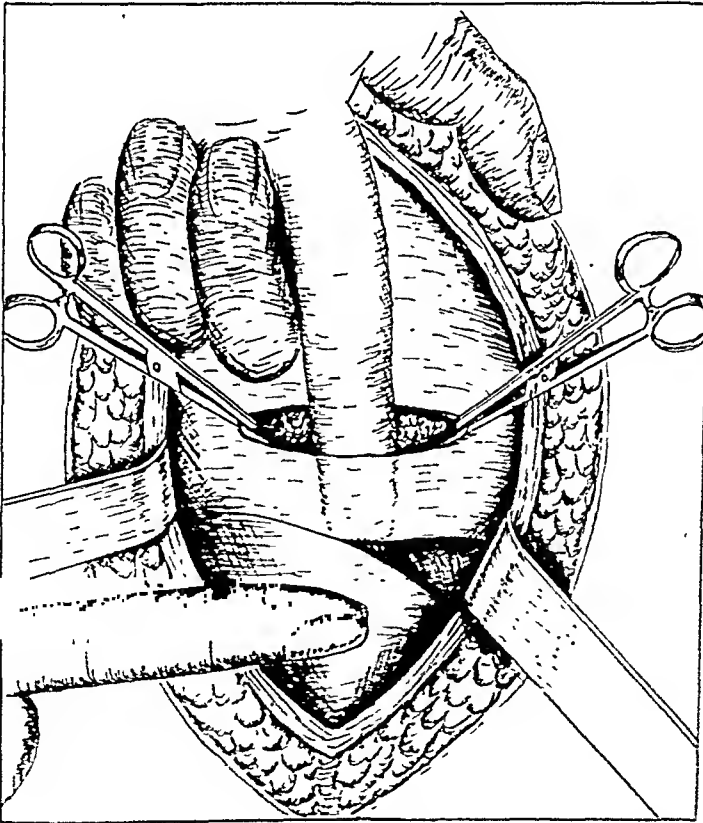


Fig. 4.—The bladder is pushed downward by the index finger of the right hand. As the strands of areolar tissue which join the vesical fascia to the peritoneum are brought to view by counter pressure with the index finger of the left hand within the peritoneal cavity, they are cut with scalpel or scissors. The top and right bladder angle is also denuded of its peritoneum.

Aldrich, C. Anderson, and Holmes, Carl A.: Treatment of Impetigo Neonatorum With Minimal Doses of Penicillin, *Am. J. Dis. Child.* 72: 279, 1946.

The authors report a series of ten infants with impetigo seen among the newly born babies in the obstetric nursery at St. Mary's Hospital, Rochester, Minn.

The routine treatment now given such infants consists of two doses of 5,000 units each at a three-hour interval as soon as the diagnosis is made.

These babies are returned to the original nursery after thirty-six hours of the beginning of treatment. No spread to other babies has occurred.

JAMES P. MARR.

Slobody, Lawrence B., Benson, Ruel A., and Mestern, Joan: A Comparison of the Vitamin C in Mothers and Their Newborn Infants, *J. Pediat.* 29: 41, 1946.

The authors report 77 mothers and their newborn infants tested with an intradermal test for vitamin C.

The newborn infant tends toward vitamin C saturation, even if it must deplete the mother. Their ability to do so is as yet unexplained. The authors advance several suggestions as possible sources.

JAMES P. MARR.

Brown, Estelle W., Lyon, Robert A., and Anderson, Nina A.: Causes of Prematurity. VII. Influence of Uterine Bleeding on the Incidence of Prematurity, *Am. J. Dis. Child.* 71: 482, 1946.

This study is based on the records of 13,329 mothers and infants, and the separate groups of mothers suffering from different types of bleeding are large enough to permit statistical evaluation of the data.

The offspring of those with placenta previa was 30 per cent. In the offspring of those with premature separation of the placenta the rate was 53 per cent. In the offspring of those who had only the mildest form of bleeding the rate was 14 per cent.

The occurrence of other illnesses, such as toxemia of pregnancy or syphilis, together with bleeding, did not increase the incidence of prematurity above the levels associated with bleeding alone.

These rates were in distinct contrast to that of 7 per cent, the rate of premature deliveries by the group of women who had no symptoms of bleeding throughout pregnancy.

JAMES P. MARR.

Holmes, Arthur D., Kuzmeski, John W., Lindquist, Harry G., and Rodman, Henry B.: Goat's Milk as a Source of Bone-Building Minerals for Infant Feeding, *Am. J. Dis. Child.* 71: 647, 1946.

Twenty-four samples of goat's milk were assayed for calcium, magnesium, potassium, phosphorus, fat, and nitrogen. The values obtained were calcium, 137 mg. per hundred grams; magnesium, 17 mg.; potassium, 170 mg.; and phosphorus 112 mg.; fat 4.4 per cent; and protein, 3.4 per cent.

While goat's milk is shown to be a rich source of minerals for infants, a final appraisal of its true value as a source of bone-building minerals for infant feeding must await data regarding the extent to which infants can utilize the minerals supplied by goat's milk.

JAMES P. MARR.



vein, the uterine artery, and uterine vein of the cotyledonary sheep placenta. These values indicated that during the nine periods of observation (81, 86, 97, 107, 110, 113, 126, 132, and 147 days of fetal age), the pressure gradient favored the movement of oxygen from the maternal to the fetal blood while the average pressure differences increased from 11 mm. Hg at 80 days to 57 mm. at 147 days.

It is unfortunate that more human data of this type are not collected at the time of hysterotomies and cesarean sections, under local anesthetics, and compiled. It might contribute much to further understandings on fetal anoxemias. C. E. FOLSOME.

Traut, Herbert F.: Hypoxemia of the Fetus, *West. J. Surg.* 54: 379, 1946.

The fetal blood in utero has a progressive drop in oxygen saturation from 50 per cent at seven months to 28 per cent at term. The stress of labor, analgesic drugs, and separation of the placenta places the fetus in a state of further oxygen want. The human placenta must provide from a single blood lake transfer of salts, sugars, gases, and amino acids. As term approaches, more amino acids are required, these pass slowly through the chorionic villus, and so circulation through the placental lake becomes slow and sluggish to permit time for amino acid absorption. This retarded circulation reduces oxygen exchange. This handicap is partially compensated for by an increased number of fetal red blood cells, increased capacity of fetal hemoglobin to carry oxygen, and by shedding of the Langhan cells to permit closer proximity of the fetal to maternal blood. Such a delicate mechanism is easily disturbed. Deterioration of the cerebral cortex follows oxygen want. In a study of 132 children who had suffered hypoxemia during labor it was found that 97 suffered alterations in behavior later in life and the other 35 showed subnormal intelligence, locomotor difficulties, and epilepsy. Administration of oxygen to the mother during labor is recommended wherever conditions arise that will contribute to the hypoxemia of the fetus. WILLIAM BICKERS.

Tyson, Ralph M.: A Fifteen-Year Study of Prematurity From the Standpoint of Incidence, Mortality, and Survival, *J. Pediat.* 28: 648, 1946.

This report consists of a fifteen-year clinical and statistical study of premature infants born in the Philadelphia Lying-In Hospital, a branch of the Pennsylvania Hospital.

Only a slight annual fluctuation in the occurrence of premature babies was evident and it could not be proved that age, race, and economic factors were determining factors, whereas there was some reason to believe that competent prenatal care, together with faithful co-operation of the pregnant woman, produced a favorable response.

The survival of premature infants seems to be primarily dependent upon their birth weight, the absence of severe complications before and during delivery, and skilful care during the first few weeks of life. The cautious administration of food, the avoidance of dehydration and infection, and the maintenance of a favorable environment are discussed.

JAMES P. MARR.

Glynn, Martin J.: Treatment of Epidemic Diarrhea of the Newborn, *J. Pediat.* 29: 205, 1946.

The author reports 91 full-term and 92 premature infants under four weeks of age treated by a specific regimen, which is carefully outlined. Of the full-term infants, the mortality was 13 per cent. Among the premature infants, the rate was 17 per cent.

JAMES P. MARR.

Jacobi, Mendel, Litvak, Abraham, and Gruber, Seymour: The Influence of Human Serum Albumin on Edema in Erythroblastosis Fetalis, *J. Pediat.* 29: 177, 1946.

The authors report two patients with erythroblastosis fetalis complicated by severe generalized edema successfully treated with concentrated human serum albumin.

It is postulated that liver damage, frequently a feature in severe erythroblastosis fetalis, with a disturbed blood protein level was the causative mechanism of the edema and that the serum albumin restored the level. JAMES P. MARR.

As long ago as 1937, our Pittsburgh group recognized these dangers, developed, and announced a nonirritating opaque medium for hysterosalpingography named Skiodan-acacia (Winthrop<sup>2-4</sup>). Both the skiodan and its vehicle, acacia solution, are completely eliminated from the body, thus not having a foreign body effect, and so rapidly does this solution disappear that the serial x-ray pictures must be taken immediately and in close sequence after injection. Accidentally injected into a vein, its elimination through the kidneys (skiodan) and the liver and bowel (acacia) would proceed so rapidly as to offset the likelihood of embolic effect. So far as I know, there has been no case of fatal pulmonary embolism reported after the use of this absorbable medium.

The third item in avoidance of such an accident is proper technique. As Ingersoll and Patterson point out, (a) hysterosalpingography should not be attempted within eight days after cessation of menses, (b) or after a curettage; (c) a short blunt tip should be used (or the soft flexible Hyam's tip). I would add that screw-thread tips are especially to be avoided, and (d) that the fractional injections according to Hyam's technique should be utilized. This is marked by serial injections of 3 c.c. each for a total of 9 c.c. with an x-ray picture after each 3 c.c. The advantages of this technique are many and so familiar that they do not need to be recounted. The likelihood of intravasation is lessened by this method as contrasted with a single forcible injection to full uterine capacity (9 to 10 c.c.).

To recapitulate, judgment in selection of cases and proper technique should eliminate this gynecologic hazard.

PAUL TITUS, M.D.

1015 HIGHLAND BLDG.,  
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MARCH 28, 1947

### References

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2. Titus, P., Tafel, R. E., McClellan, R. H., and Messer, F. C.: AM. J. OBST. & GYNEC. 33: 164, 1937.
3. Titus, P., Tafel, R. E., McClellan, R. H., and Messer, F. C.: AM. J. OBST. & GYNEC. 36: 889, 1938.
4. Titus, P., Tafel, R. E., McClellan, R. H., and Messer, F. C.: AM. J. OBST. & GYNEC. 37: 495, 1939.

### Curare in Dysmenorrhea

*To the Editor:*

In my article on this subject, published in the April, 1946, issue of the JOURNAL, I misstated the dosage of Intocostrin employed. The correct dosage of Intocostrin or solution d-tubocurarine ehloride, (Squibb), used by Dr. Danielson and myself for the relief of dysmenorrhea is one half to one c.e. and not 50 to 100 units or milligrams as incorrectly stated by me.

Abbotts are now making a solution d-tubocurarine ehloride of the same activity per c.e. as the Squibb preparation, but containing 3 milligrams per c.e.

Curare should not be given to anyone with weakness of the throat muscles (myasthenia gravis), and intravenous doses larger than 1 to 1½ c.e. should not be given without apparatus available for artificial respiration.

FLORENCE JOHNSTON, M.D.

CEDAR RAPIDS, IOWA  
APRIL 7, 1947

## Correspondence

### Oil Embolism From Hysterosalpingography

*To the Editor:*

The frequency of accumulating reports of oil emboli, fatal and otherwise, following the injection of iodized oil for hysterosalpingography is alarming and serious, particularly because this accident is almost entirely uncalled for.

The latest of these occur in the article by Ingersoll and Robbins<sup>1</sup> in the February (1947) issue of this JOURNAL. T. R. Hannon of Houston, Texas, has recently sent me reports of two similar cases about which he was consulted. One was fatal.

In the first place, altogether too many hysterosalpingographies are being performed. This procedure should not be substituted, as so many do, for tubal insufflation (the Rubin test), but should be restricted to those patients in whom the desired information cannot be obtained by the Rubin test.



Fig. 1.—Hysterosalpingography with iodized oil embolism. Pelvic veins invaded, probably through back pressure against obstructed tubes. Screw-tip cannula may damage endocervix or endometrium making point of entry into veins. (Courtesy T. R. Hannon, M.D.)

Secondly, iodized oil should not be used as the opaque medium because it is a foreign body remaining as such wherever it is injected. It is not absorbed and eliminated, but remains encysted within the pelvis when passed through the tubes, or becomes a highly dangerous embolic agent if accidentally injected into a vein. Moreover, it is likely to act as a chemical irritant of the tubes in persons sensitive either to iodine, or to its vehicle, the poppy-seed oil.

The following newly certified physicians are included in the list of diplomates of the American Board of Obstetrics and Gynecology: Dr. Carl Samuel Bickel, Central Union Bldg., Wheeling, West Virginia; Dr. Elmer M. Broen, 313 Bernard Ave., Richland, Washington; Dr. Carl Rex Moe, 316 Henrietta Street, Kalamazoo, Michigan.

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### University of California Medical School Postgraduate Courses

The University of California Medical School, in association with University Extension, University of California, announces a course in the applications of nuclear physics to the biological and medical sciences to be given at the Medical Center, in San Francisco, from June 30 through July 18, 1947. It will consist of didactic lectures, laboratory demonstrations, and seminars for round-table discussions, and will be open to individuals in the fields of medical and biological research.

Requests for detailed information to be addressed to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

STACY R. METTIER, M.D.

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The University of California Medical School, in association with the Medical Extension, announces the following postgraduate courses:

1. Course in gynecological and obstetrical pathology, and in smear technique as it pertains to cancer of the uterus, stomach, urinary tract, and lungs: August 4 to 15, inclusive, 1947, daily at 9:00 A.M. to 4:30 P.M.

NOTE: This course is limited to 75; registrants are to furnish their own microscopes, of good quality.

Either the morning or the afternoon sessions may be taken, alone or together. It is suggested that experience with the microscope and in cancer diagnosis in general will be an essential prerequisite if one is to obtain proficiency and confidence in the judgment of the smear preparations.

This course is designed to fulfill two needs: (a) requests from physicians who wish to prepare for the American Board Examinations, and (b) requests from pathologists, cytologists, researchers, and all others who are interested in learning to use the smear technique for the diagnosis of cancer in various parts of the body.

2. Obstetrics and gynecology: September 1 to 5, 1947, at 9:00 A.M. to 1:00 P.M., and 2:00 to 5:00 P.M.

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### American Gynecological Society Meeting

The American Gynecological Society will hold its meeting at the Seigniory Club, Montebello, Quebec, on June 16 to 19, 1947. This announcement was omitted in the April issue of the Roster.

# Items

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## American Congress on Obstetrics and Gynecology

Three panel-type morning sessions on the following subjects have been arranged:

1. *Anesthesia and Analgesia*, Tuesday, September 9, Dr. Nicholas J. Eastman, Chairman, with the cooperation of Dr. J. P. Greenhill, Chicago; Dr. John Adriani, New Orleans; Dr. Stuart Cullen, Iowa City; and Dr. Arthur Baptisti, Hagerstown.

2. *Cancer*, Wednesday, September 10, Dr. Robert A. Kimbrough, Philadelphia, Chairman, with the cooperation of Dr. John Randall, Iowa City; Dr. Charles L. Martin, Dallas; Dr. Joe V. Meigs, Boston; and Dr. Herbert Schmitz, Chicago.

3. *Cesarean Section* on Thursday, September 11, Dr. Edward Schumann, Philadelphia, Chairman, with the cooperation of Dr. Edward G. Waters, Jersey City; Dr. Edward Davis, Chicago; Dr. E. D. Plass, Iowa City; and Dr. William Benbow Thompson, Hollywood.

The afternoon meetings of the Medical Section of the Congress will consider the Psychosomatic Aspects of Pregnancy on Tuesday; Pregnancy Complicated by Heart Disease, Diabetes, and Tuberculosis on Wednesday; and Recent Advances in Endocrinology on Thursday.

Round table discussions from 4:00 to 5:00 P.M. daily will consider such topics as abortions, asphyxia, fibroids, prolonged labor, infertility, early ambulation, uterine bleeding, nutrition in pregnancy, endometriosis, the Rh factor, erythroblastosis, geriatric gynecology, and other pathologic conditions relating to obstetrics and gynecology.

Concurrent round table sessions will be held for nurses, hospital administrators, and public health workers.

A scientific and educational exhibit under the direction of Dr. J. P. Pratt of Detroit and a comprehensive motion picture program under the guidance of Dr. John Parks of Washington are in process of development. Those wishing to make applications for space in these exhibits, especially for time on the cinema program, are urged to make early application. Necessary blanks may be obtained from the office of the Congress, 24 West Ohio Street, Chicago 10, Illinois. Better hurry!

On Friday, the last day of the Congress, the entire morning will be given over to the program of the National Federation of Obstetric-Gynecologic Societies. Dr. James S. Taylor of Altoona is arranging this session.

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## American Board of Obstetrics and Gynecology, Inc.

### Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pa., by the entire Board from Sunday, June 1, through Saturday, June 7, 1947. The Hotel William Penn in Pittsburgh will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel William Penn.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Applications are now being received for the 1948 examinations. For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

- CALKINS, L. A., The second stage of labor; internal rotation, 488
- CALLENDER, CLAUDE G. (WITH BEACHAM, WOODWARD D., HOLMES, JOHN A., BEACHAM, HUGH T., MITCHELL, GEORGE J., AND BEACHAM, DAN W.), A 55-pound solid uterine myoma, 839
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attached to the peritoneum from the fundus of the bladder to the vesico-uterine pouch. If desired, one can also utilize the paravesical approach of Norton. Some men may choose to utilize a combination of the Norton, the Waters, or the above-described approach. However, the beginner must remember that there will be less danger of injury to the bladder, and that there will be less bleeding from the vesical vessels, if the peritoneum alone is dissected off. If some vesical fascia comes off during the dissection, it is allowed to remain attached to the peritoneum. The bladder is now pushed downward and to the right; exposing the fascia covering the lower uterine segment. This is incised about three-fourths of an inch inferior to the zone of peritoneal reflection. The incision of the lower uterine fascia should extend equally on both sides of the midline. It should be larger than the proposed lower uterine incision, and care

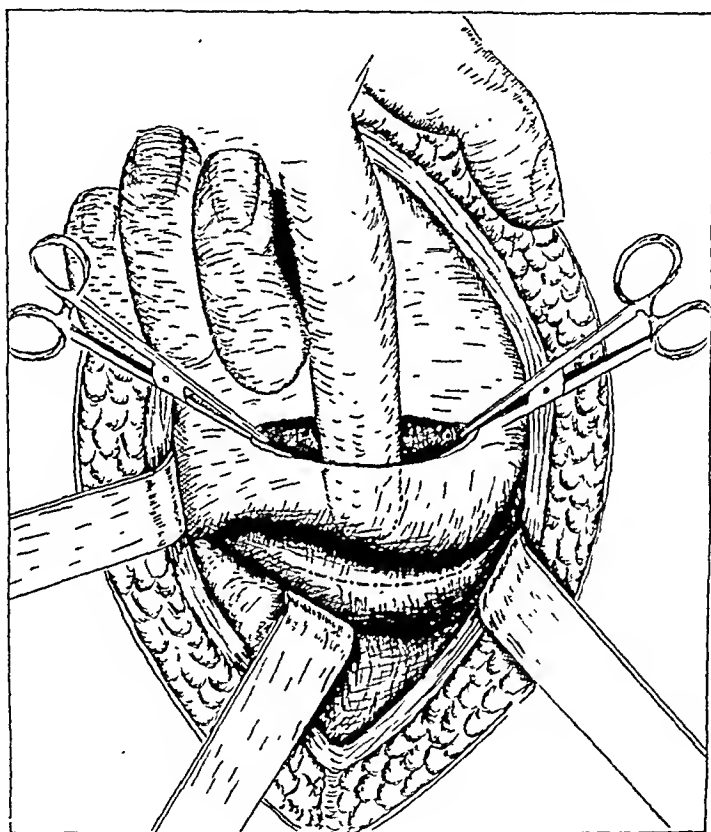


Fig. 5.—The bladder has been completely denuded of its peritoneum. The tongue-like hernial sac can be plainly seen throughout its course by inserting the index finger within the peritoneal cavity. By pushing upward on this fold and pushing downward and to the right on the bladder, the lower uterine segment covered with its fascia is seen. The type and position of the incision through the fascia is shown.

should be taken that only the fascia is incised (Fig. 5). A finger is inserted beneath the upper flap of fascia and bluntly dissected upward for a short distance, carrying with it the tongue-like peritoneal fold. The lower fascial flap is similarly pushed downward with the bladder. This incision of the uterine fascia over the lower uterine segment gives the operator increased mobility of the uterine peritoneum, and the bladder can be pushed downward with ease so that it will be out of the way. This incision also exposes a relatively large area of the lower uterine segment through which a central nick is made with the point of a scalpel about one inch above the detached bladder. With bandage scissors, this nick is enlarged in crescentic fashion, ends curved upward, starting from the left, then proceeding to the right. The ends of this incision may reach one and one-half inches above the apex of the curve. This incision should be large

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enough to admit the closed fist with ease (Fig. 6). All retractors are now removed, and the baby extracted manually, by forceps or vectis, or by version and breech extraction, depending upon the choice of the operator. The writer prefers extraction by the breech in the vast majority of the cases. Ergotrate,  $\frac{1}{160}$  grain, is given intravenously and the placenta extracted manually at once. The lower uterine segment is closed by three layers of continuous chromic catgut sutures No. 2. The bladder is anchored to its former position beneath the transversalis fascia. The peritoneal opening is raised in tent fashion and a plain catgut suture is tied around the base of the tented peritoneum. To secure this suture from slipping, the peritoneum distal to it is transfixed. This is done by

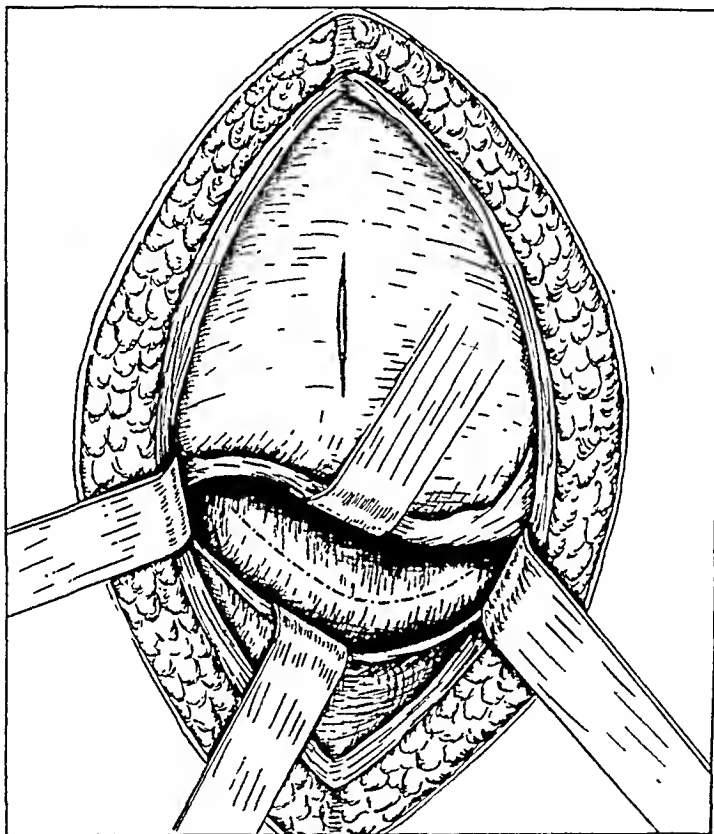


Fig. 6.—After incising the fascia of lower uterine segment, a finger is inserted under the upper flap of fascia, and, by pressure, this part of the fascia with the peritoneal tongue is raised off the lower uterine segment. A finger is inserted under the lower fascial flap pushing with it the bladder downward and to the right, exposing a fairly large space through which a crescentic incision is made.

passing the needle through the distal peritoneum from above downward and again from side to side. This procedure secures the first suture from slipping and has the advantage of closing off the peritoneal cavity without having any needle holes or sutures within the abdominal cavity. This closure of the peritoneum may be performed before the lower uterine segment is incised if the patient has been in labor, or it may be performed afterward in selective cesarean sections. The abdominal wall is closed by whatever method the surgeon prefers.

The primary purpose of this article is to describe the technical details of a new type of cesarean section which, I hope, will replace the highly popular two-flap type of cervical cesarean section. Although I do not like to tire the reader with statistics, it is fair to record my results in 19 cases, and then compare

these with 19 consecutive two-flap cesarean sections. Table I is a record of 19 low flap operations; while Table II is a record of 19 cesarean sections performed by the technique described. There were no fetal or maternal deaths in either group.

The operating time in the group in Table I averaged twenty-nine minutes. It will be noted that in two cases the operating time exceeded forty minutes. In Case 4, two subserous fibroids were removed. In Case 16, a tubal ligation was

TABLE I. RESULTS OF TWO-FLAP TYPE OF INTRAPERITONEAL CESAREAN SECTION

CASE	NAME	AGE (YR.)	OPERATING TIME (MINUTES)	DAYS IN HOSPITAL	MORBIDITY	DIS- TENTION	URINARY COMPLAINTS
1	E. O.	31	32	11	0	0	0
2	E. L.	35	30	13	0	0	0
3	M. C.	34	19	10	2 days	2 days	Unable to void —2 days
4	A. A.	32	47	11	1 day	2 days	0
5	M. B.	35	26	11	1 day	0	0
6	M. F.	29	35	11	0	0	0
7	M. G.	27	25	10	0	0	0
8	R. D.	30	27	10	0	0	0
9	L. P.	26	25	10	0	0	Unable to void —1 day
10	J. B.	27	23	10	0	0	0
11	A. C.	26	33	11	7 days	0	Burning on urination
12	A. M.	30	19	10	0	2 days	0
13	A. S.	24	23	12	3 days	0	0
14	S. M.	29	29	10	0	0	0
15	E. O.	33	27	11	0	2 days	0
16	A. M.	40	43	11	0	0	0
17	A. C.	25	34	11	0	2 days	Burning on urination
18	M. M.	33	27	10	0	0	0
19	C. L.	30	27	11	0	1 day	0

TABLE II. RESULTS WITH MODIFIED EXTRAPERITONEAL CESAREAN SECTION

CASE	NAME	AGE (YR.)	OPERATING TIME (MINUTES)	DAYS IN HOSPITAL	MORBIDITY	DIS- TENTION	URINARY COMPLAINTS
1	M. T.	26	29	9	0	0	0
2	A. F.	26	21	10	0	0	0
3	P. C.	29	35	10	0	0	0
4	E. M.	20	40	10	1	0	0
5	J. A.	24	33	10	1	0	0
6	M. C.	28	35	11	1	0	0
7	E. I.	26	35	9	0	0	0
8	P. N.	24	40	11	2	0	Unable to void —1 day
9	M. D.	29	40	9	1	0	0
10	A. Z.	20	40	10	0	0	0
11	A. C.	25	44	11	0	0	0
12	M. C.	34	35	10	0	0	0
13	M. B.	29	25	11	1	0	0
14	H. M.	34	45	9	0	0	0
15	C. M.	37	49	10	1	0	0
16	A. D.	26	32	9	0	0	0
17	F. O.	28	40	9	0	0	0
18	F. F.	30	32	10	0	0	0
19	M. S.	29	32	10	0	0	0



called upon to do a Latzko or a Waters operation in frankly infected or neglected cases.

8. This operation is not intended to replace the Latzko nor the other strictly extraperitoneal operations, which are technically more exacting to perform and unquestionably safer than any type of operation in which the peritoneal cavity is opened. However, it does enable the operator to perform ligation of the tubes and allows him to inspect the uterus and adnexae without detracting from the merits of the operation. This advantage is missing in the extraperitoneal operations.

9. The amount of space available for the delivery of the baby is decidedly greater by this method than by the Latzko, the Waters, or the Norton operations. In fact, it gives as much space as is available in the intraperitoneal, two-flap type, cesarean. At no time should the operator have to resort to the use of forceps to deliver the head because of restricted space. It has been my practice to do routine internal podalic version on all vertex cases to deliver the babies. The uterine wound will not tear, as a rule, if the initial incision into the lower uterine segment has been made large enough, i.e., large enough to easily admit the closed fist.

10. The amount of time necessary to perform this type of operation should not exceed that taken to perform an intraperitoneal, two-flap type, by more than five minutes. It should not take over thirty to thirty-five minutes.

11. There is less danger of injuring the bladder or of repeatedly buttonholing the peritoneum because the separation of the bladder from the peritoneum is aided by counter pressure of the internal fingers. The dissection is at all times under direct vision. There is never any need to guess where the vesico-uterine fold or tongue of peritoneum is located. It can be easily seen at all times. It is not necessary to distend the bladder with methylene blue solution. In fact, the operation can be more easily performed when the bladder is collapsed.

This simple modification of the cervical cesarean section by eliminating the use of flaps, is, I believe, a distinct improvement, and I feel that this method has much to offer those who care to perfect themselves in its performance. I have no doubt that other obstetricians have done this operation in some modified form, but when the above technique is followed and tried by different surgeons, I believe it will be preferred by many as the operation of choice in elective cesarean section.



performed. In addition, tubal ligations were also performed on Cases 1, 2, 6, and 17. If we make allowances for the time consumed in performing these additional operations, the average time would be reduced to twenty-five minutes. The average hospital stay in Group 1 was 10.8 days. In this group, abdominal distention was seen in six patients and urinary complaints were present in four.

The operating time in the group in Table II averaged thirty-six minutes. It will be noted that in three cases the operating time exceeded forty minutes. In Case 11 a huge pedunculated subserous fibroid was removed. In Case 14, a large adherent chocolate cyst, the size of an orange, was removed from the right ovary. In Case 5, a bilateral tubal ligation was performed. If we make allowances for the time consumed in performing these additional operations, the average time would be reduced to thirty-two minutes. The average hospital stay in Group 2 was 9.8 days. Not a single patient of this group had postoperative distention and only one patient was unable to void for one day only.

Comparing the results of these two groups, we note that the operating time averaged thirty-two minutes in Group 2, and twenty-five minutes in Group 1. The extra time spent in Group 2 was more than compensated by the shorter hospital stay of one day, freedom from abdominal distention, and the almost complete absence of urinary tract complaints.

### Advantages

1. Instead of making two separate peritoneal incisions, only one is utilized. The extent of the parietal incision will become minimal as the operator gains experience. When this incision is closed in the manner described, no raw surfaces, suture material, or needle punctures are present in the peritoneal cavity. This should minimize the possibility of postoperative adhesions.

2. The greatest danger of cesarean section is still infection. Seepage, when it does occur in the intraperitoneal cervical cesarean section by the flap method, must still be into the general peritoneal cavity. By this method, seepage or uterine wound breakdown will be extraperitoneal.

3. At no time during the operation does the bowel come into view. Sponges in the abdomen are therefore unnecessary, hence eliminating the possibility of postoperative distention.

4. A careful checkup of all cases after the uterine wound has been closed to determine the possibility of peritoneal contamination by spill of blood or amniotic fluid revealed that practically no fluid had entered.

5. The cervical wound can be placed low enough, i.e., two inches below the point of reflection of the vesico-uterine peritoneum. This makes the operation a truly cervical one and not a low fundal one as I have seen it done many times. The wound is thus placed in that portion of the uterus that is noncontractile and hence is more likely to be at rest. The wound is thus placed in that portion of the uterus which stands infection best.

6. This operation can be used routinely in place of the low-flap method, regardless of whether the patient has been or has not been in labor, and also regardless of how deeply the vesico-uterine fold of peritoneum extends behind the pubes. This is a highly desirable advantage.

7. This familiarity with the anatomy of the cervical and vesical fascias and with the vesico-uterine septum gives the operator added confidence when he is

One patient I saw developed a phlebothrombosis secondary to a degenerating fibroid. Thrombectomy was performed, and two weeks later a hysterectomy was performed. At the time of the hysterectomy, the surgeon noted that the iliac vein was free from any thrombosis, whereas the pelvic veins coming from the uterus showed definite evidence of phlebothrombosis.

Another patient had a normal delivery. Twelve days later, she developed a phlebothrombosis of the left leg. The femoral vein was exposed; a clot was sucked out well upward into the pelvis. Free bleeding occurred. Her temperature and pain immediately subsided, and the patient went home. Four weeks later, she had an attack of phlebothrombosis in the right leg and was returned to the hospital. A clot was sucked out of this leg and the femoral vein was ligated. It does not seem likely that, during this period, there was a residual clot that extended upward into the vena cava, as the patient had had no pain, no tenderness, and the swelling in her left leg had completely subsided. There must, however, have been an extension from the pelvic veins of the uterus, which created the second attack.

These observations occurring in phlebothrombosis in women who are pregnant, or secondary to hysterectomy, have made me alter my plan of attack somewhat, as I shall describe later when we come to the problems of treatment. I will state now, however, that I believe in cases of embolism occurring in gynecologic or obstetric conditions, the femoral vein should be exposed and the emboli sucked out higher up in the pelvis, even if there is no evidence of thrombosis in the femoral vein.

Before discussing the individual problems that occur in obstetrics and gynecology, I should like to review very briefly the use of anticoagulants. There are three main anticoagulants now in use:

*Sodium thiosulfate.*—In 1928, at the Fifth Avenue Hospital, Dr. Stanley-Brown and I began our early experimental work on thrombosis and embolism, and we were looking for an anticoagulant which might be given as a therapeutic measure to prevent thrombosis and embolism. We consulted Dr. Charles Loeb, who was professor of pharmacology at Columbia University, and he suggested sodium thiosulfate. He had used it in dogs to prevent extra corporeal clotting. We didactically started to use the routine injection of sodium thiosulfate. Since that time, considerable experimental work has justified our impression that it had anticoagulant properties. The possible rationale for the use of sodium thiosulfate is described by Jorges and Bergstrom, who state that the anticoagulant activities of different heparin preparations obtained in a similar manner from the liver vary in their sulfur contents. Preparations of liver heparin containing from 7 to 12.26 per cent of sulfur show anticoagulant potencies varying from 45 to 160 per cent of the standard heparin from which they are derived. Heparin is largely produced by the mast cells in the intima of the blood vessels, and it is possible, therefore, that the sulfur element of sodium thiosulfate may increase the anticoagulant activities of the heparin which is liberated in the blood stream.

In a large series of cases at the Fifth Avenue Hospital, we were able to show that we had diminished the incidence of thrombosis and embolism in cases where we suspected that there might be an accident. Our suspicions at that time were based on the increased prothrombin and fibrinogen in our routine studies

## THE SURGICAL TREATMENT OF PHLEBOTHROMBOSIS IN OBSTETRIC AND GYNECOLOGIC PATIENTS\*

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**B**EFORE discussing the treatment of phlebothrombosis as it occurs in obstetrics and gynecology, it is wise to define the two types of lesions in the veins as met with in the above-named specialties.

1. *Thrombophlebitis*.—Thrombophlebitis, as the name indicates, is a phlebitis and periphlebitis sometimes associated by an absence of a clot in the lumen. It is usually initiated with a chill, high temperature, swelling of the leg, marked tenderness, and often redness over the course of the involved veins. It is characterized very largely by a perilymphatic involvement as well as involvement of the walls of the vein. Embolism following thrombophlebitis is relatively rare. It occurred in 10 per cent of the Toronto series, and in about 12 per cent of the cases analyzed by the Mayo Clinic.

2. *Phlebothrombosis*.—Phlebothrombosis is characterized by a blood clot which fills the lumen of the vein. The onset may be sudden. It is not accompanied as a rule by as high an elevation of temperature nor with as great swelling of the legs as in thrombophlebitis. Homans has shown experimentally that if one wishes to create the so-called "alba dolens" in experimental animals, it is necessary to destroy the lymphatics. Mere ligation of the vein will not, as a rule, create swelling.

Frequently, the diagnosis is not made until a pulmonary embolism has been discovered. I believe that in gynecology and obstetrics, the diagnosis of phlebothrombosis is much more difficult than it is in general surgery. In the general surgical patient, the thrombus usually starts in the deep veins of the calf. The following clinical findings will make one suspicious that thrombosis is present and that embolism may occur:

Homans has drawn attention to the fact that the greatest danger of thrombosis and embolism lies in the deep veins of the calf, and that if the foot is hyperextended, causing extension of the gastrocnemius, the patient often complains of pain in the calf, whereas lying normally, he is unaware of it. Also, I have found by comparing the two calves, with the knees in semiflexion and the patient on his back, that the affected leg gives one an impression of more resistance in compressing with the fingers the gastrocnemius muscle against the posterior surface of the tibia. Any swelling of the thigh is more easily detected, as usually the patient complains of some tenderness in the region of Poupart's ligament. Careful palpation will reveal a pencil-like cord behind the femoral artery. These clinical signs are well worth noting in patients with unexplained temperature.

On the other hand, in obstetrics and gynecology, the thrombus very frequently starts in the pelvic veins, and emboli may occur before there is any manifestation of thrombosis in the extremities.

\*Read (by invitation) at a meeting of the New York Obstetrical Society, May 14, 1946.

My observations of Loewe's method show that it does lengthen the bleeding time, and that the patient has no ill effects from the treatment save for the pain in the injection area. This tenderness in the area where the heparin-Pitkin solution is injected becomes quite a problem, as the patient may, about the time of the third injection, oppose the injection because of the pain involved. As the process is improved, however, I feel certain that this one difficulty will be remedied. To those who have had to give heparin constantly for from five to ten days, this method is a great improvement. The expense of the old method, and the amount of fluid given during each 24 hours, almost make continuous injection prohibitive in these days of diminishing nursing care.

The results of Loewe's treatment are that it is possible now to heparinize a patient for ten days at much less expense and with possibly three to four subcutaneous injections during this time.

*Dicumarol*.—This is a compound which occurs in spoiled sweet clover silage, and it was discovered in the study of sweet clover diseases which caused the hemorrhagic diatheses in cattle from the ingestion of spoiled sweet clover hay.

Link and his co-workers completed the isolation and synthesis of dicumarol in 1940. Lately, it has been used in various clinics as a possible substitute for heparin. It has the advantage that it is relatively cheap, that it can be given by mouth, and that it produces a prolongation of the prothrombin and coagulating time. Its disadvantages are that it takes from twenty-four to thirty-six hours before it begins to show its antieoagulant effect, and that the action may continue several days after the drug itself has been discontinued. Experimental study shows that it causes a widespread dilatation of the superficial vessels but no lesion of the vessel walls, and does not create liver necrosis.

Dicumarol is being used more and more extensively by all observers. It has disadvantages in that it is hard to control if hemorrhages should occur following its use. However, Willard Parsons has recently reported the control of the hemorrhagic tendencies following the use of dicumarol by administration of vitamin K. If this is possible, it makes the drug much safer. Previously, it has been thought that only transfusions would in any way control its hemorrhagic tendencies.

Prophylactically, dicumarol is given in many clinics and, so far, with many promising reports. In my own experience, I have never seen a case of thrombosis or embolism occur after the use of intravenous sodium thiosulfate when administered prophylactically. I think it is less dangerous and more controllable.

### Treatment

During pregnancy, there are patients who develop either localized subcutaneous attacks of thrombophlebitis in the veins in the calf, or the process may extend upward along the long saphenous vein. These attacks occur frequently in patients who have had varicose veins before they become pregnant. I believe that in these patients, a proximal ligation of the long saphenous vein, which may be done under local anesthesia either at home or in the hospital, may save the patient considerable distress and some danger at term. It is interesting to note that if a segment of vein is taken out, the pain almost immediately disappears in the involved vein, often quite a distance distally from

of the blood clotting factors. Since that time, it has been my custom to use sodium thiosulfate whenever a patient has been moderately distended, whenever there is a continued slight elevation of temperature, and whenever I fear an accident. In cases so treated, I have never had thrombosis or embolism develop. It is my custom to inject 10 c.c. of a 10 per cent solution of sodium thiosulfate intravenously for several days in succession. The drug is cheap, apparently it has no toxic effect, and it is not particularly annoying to the patient.

*Heparin.*—If thrombosis has occurred, I do not believe that sodium thiosulfate compares in any way with either heparin or dicoumarol. You are all aware of the continuous intravenous therapy with heparin. You know its expense, the difficulties to the patient of having a continuous intravenous solution during several days, and the dangers of hypoproteinemia from too much intravenous fluid. If heparin is given intravenously, it has to be given continuously, because its anticoagulant effects cease within two or three hours after the injection has been discontinued. Patients have been seen who have developed thrombosis or embolism following the discontinuance of the use of heparin.

Recently, a newer method for heparin treatment has been developed by Loewe. I should like to describe his method of using heparin subcutaneously by injections at two- to three-day intervals. I quote from Loewe as follows:

“To accomplish a slower and more equitable absorption of heparin, the Pitkin menstruum was adopted as a vehicle. This menstruum was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. The ingredients are gelatin, 15 to 30 per cent; dextrose, 5 to 12 per cent; acetic acid, 1 to 1.5 per cent; distilled water, as much as will suffice to make 100 per cent. The viscosity of the menstruum, which is predicated on the concentration of the gelatin and dextrose, determines the rate of liberation of the drug; the greater the viscosity, the slower the liberation. In the preparations containing heparin, the optimum percentages of gelatin and dextrose were 18 per cent and 8 per cent, respectively.

“Ampules containing varying proportions of heparin and Pitkin menstruum, with or without vasoconstrictor elements, were prepared. All ingredients apart from heparin were found to be inactive in control tests.

“The contents of the ampules were liquefied at 110° F., drawn up through a 2.5-inch 19-gauge needle into a previously warmed, sterile 5 c.c. or 10 c.c. syringe and immediately injected subcutaneously, preferably in the anterior or lateral aspect of the thigh. Intragluteal injections were also done in a limited number of instances. Although this method of administration was abandoned because of too rapid absorption, further experience may eventually prove it to be just as effective as by the subcutaneous route. When two ampules were employed, the contents were thoroughly admixed in the syringe before injecting. The material coagulated promptly following inoculation. The injections were administered with a minimal amount of discomfort to the patient. Some patients subsequently complained of pain, tenderness, and swelling at the site of inoculation, particularly when a large amount (3 to 4 c.c.) of the menstruum was used. This, however, did not prove to be a deterrent to further treatment, and symptoms promptly subsided upon cessation of therapy.”

fidant that a small piece of thrombus did ascend upward into his thorax. In no other case have I seen any evidence of any such occurrence.

2. Will not the thrombus recur above where the ligation has been performed?

In order to prevent this occurrence, it has been the custom of Homans and others to administer anticoagulants after the thrombectomy. On the other hand, Allen and his group, working at the Massachusetts General, have not used anticoagulants as a routine and have not had any severe recurrence of thrombosis after ligation and thrombectomy.

3. Is there a residual swelling of the leg following ligation of the femoral and long saphenous veins?

In the large majority of cases, there is no residual swelling. I have had two patients who had persistent swelling two to three months postoperatively. One of these patients is now actively playing tennis, so that I know the swelling has largely decreased. The other patient, a recent case, had very marked swelling for three weeks postoperatively. He had a hematoma in his incision and a moderate amount of inflammatory process, which I believe interfered with his lymphatic drainage. Recent reports from his doctor state that this swelling has markedly decreased. If it should persist, I believe that lumbar sympathetic block would hasten the disappearance of the edema.

I should like to review briefly the cases on which I have performed thrombectomy in gynecologic and obstetric cases. I have performed two preoperative thrombectomies in preoperative gynecologic cases. I have performed two thrombectomies in postoperative gynecologic cases, and three in obstetric post partum. I should like to review these histories briefly and then analyze my impressions after this small series of cases:

CASE 1.—A 68-year-old female, with a large ovarian carcinoma, had evidence of a thrombus in her right femoral and saphenous veins. At the time of operation, a thrombus was removed from her right iliac vein, and then a bilateral oophorectomy for tumors the size of a football was performed. She died on her fifteenth postoperative day from renal failure. There was no residual swelling of the leg or signs of pulmonary condition. No autopsy was obtained.

CASE 2.—A woman, 46 years of age, had been seen by a gynecologist, who recommended hysterectomy for an extremely tender uterine fibroma which was fixed in the lower portion of the pelvis. The uterus extended midway to the umbilicus. Ten days later, while awaiting operation, acute phlebothrombosis occurred in the left femoral vein. I was called to see the patient at this time. There was no evidence then of pulmonary embolism. It was felt, however, that this patient would need hysterectomy in the near future because of a degenerating fibroid, and that it would be advisable to be sure that the clot was removed from the iliac vein. The clot was sucked out from the left iliac vein, and she was treated postoperatively by subcutaneous injections of heparin. Two weeks later, while still under heparinization, a supracervical hysterectomy was performed. The iliac vein was palpated and there was no evidence of any clot in its lumen. There were, however, some old thrombi in the veins of the broad ligament. This patient's convalescence was uneventful. She left the hospital two weeks after the hysterectomy.

CASE 3.—A woman 53 years of age had had a supravaginal hysterectomy performed by another surgeon four weeks previously. For the previous two weeks before I saw her, she had had pulmonary embolic seizures, confirmed roentgenologically, and by Dr. James Miller and Dr. Harold Hyman. There

where the vein is ligated. In cases where women suffer from migratory phlebitis or from recurring attacks of phlebitis, particularly where it is superficial in the veins of the calf, it is well to look between the toes to be sure there is no epidermophytosis. This is a frequent cause of recurrent phlebitis. Irving Wright in New York believes that it is probably due to a virus, while Miller, who works in New Haven, believes that it might be allergic in character, it is a cause of constant recurring phlebitis, and an attempt should be made to clear up the epidermophytosis. Frequently, we do not think to look between the toes in these patients.

The obstetrician is frequently faced with this problem: The patient has had phlebothrombosis in a previous pregnancy, and is this likely to recur in the following one? What prophylactic measures should he institute?

If the previous pregnancy has been complicated by a phlebitis of the long saphenous vein, proximal ligation may be advisable. If it was accompanied by a deep femoral phlebitis, dietary measures and the use of anticoagulants pre-partum and after five or six days post partum may be of great help. It is hard to evaluate how much help these prophylactic measures are, because often a patient has had phlebitis in the first pregnancy, and has not had any in later pregnancies without any prophylactic therapy. My suggestion, however, would be that 5 or 6 days before delivery, sodium thiosulfate should be used intravenously; and after five days post partum, in order not to increase postpartum bleeding, either sodium thiosulfate or dicumarol can be administered. The same method of approach may be used in gynecologic patients who are forced to have an operative procedure and have had a previous history of phlebothrombosis either following pregnancy or after a previous operation.

*Treatment After Phlebothrombosis Has Been Recognized Post Partum or Postoperative.*—There are three therapeutic measures which may be used, and they are:

1. Proximal ligation or thrombectomy.
2. The use of anticoagulants.
3. Injection of the first, second, third, and fourth lumbar ganglia as described by Leriche and Ochsner.

*Proximal Ligation or Thrombectomy.*—It is only fair to state before I begin the discussion of the treatment of phlebothrombosis, particularly when there has been an antecedent embolism, that I am strongly in favor of the operative approach and I shall attempt to give my reasons during this discussion.

The term proximal ligation means that one is able to ligate the vein proximal to the location of the thrombus, and thrombectomy means that if the femoral vein or the long saphenous vein are exposed just below Poupart's ligament and the clot extends upward into the iliac vein, the vein is opened and the clot is removed by suction until free bleeding occurs.

I believe there is very little discussion about the problem of proximal ligation. We will agree that this is feasible and that very little risk is entailed, and I shall not make any analysis of the cases that I have done this procedure on, except to state that I have had no mortality following its use.

The problem of thrombectomy is readily open to debate. One may ask the following questions in considering thrombectomy:

1. Is there not danger in removing the clot of breaking off the clot and having it extend upward into the vein?

Yes. In the 20 cases on which I have performed thrombectomy, I have had one patient who, during the process of sucking out the clot, became a little short of breath and looked a little cold and sweaty. The next day, however, his chest signs were negative and he was in no respiratory distress, but I am fairly con-



of the involved side is sufficient. I have had no cases that occurred as a complication of general surgery, such as gall bladders, hernias, etc., that have needed bilateral ligation or where a second surgical procedure on the other side had to be done.

### Conclusions

Lumbar sympathetic block has been popularized by Alton Ochsner and his associates in the treatment of venous occlusion in the extremities. Certainly in thrombophlebitis, with elevation of temperature, where there is not much risk of embolic formation, this procedure relieves pain and hastens the convalescence of the individual. On the other hand, where phlebothrombosis is present and there is danger of pulmonary emboli, it is my firm conviction that the operative approach and ligation of the vein is safer than relying upon the use of anticoagulants or lumbar sympathetic block. While Murray and others have reported excellent results from the use of anticoagulants without operative interference, I think that the convalescence of the patient is safer and shortened by either proximal ligation or thrombectomy. Many of us have seen emboli occur shortly after the cessation of heparin therapy.

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was fluid at the right base. The left calf and thigh were moderately swollen. She was operated upon. Under local anesthesia, the femoral vein was exposed. It was occluded with clot, but the long saphenous vein was not involved. The clot extended upward about 7 inches in the iliac vein. The same operative procedure was carried out, but, in addition, she had a lumbar ganglion block with novocaine. She had a moderate infection of the fat at the operative site in the thigh. She was given heparin subcutaneously by Loewe's method. Her convalescence was uneventful, and she had no residual swelling.

CASE 4.—This patient had a supraumbilical hysterectomy three weeks previously. During the past week, she had had three definite small pulmonary emboli. The left femoral vein contained a thrombus extending well above the inguinal ligament. A long thrombus above Poupart's ligament was removed by suction. She was treated by subcutaneous heparin. She had some residual pain in the leg for three weeks. The swelling in the thigh and leg rapidly subsided.

CASE 5.—This patient had a normal delivery of a child on April 19, 1944. On April 25, swelling was noted in the left leg and thigh, and she had an attack of pain in the chest on May 9. The patient was kept in bed and treated with rest. On May 15, pain and swelling appeared in the right leg, and the patient had another attack of pain in the chest. Under local anesthesia, both veins were exposed, and a clot was sucked out of each long saphenous and each femoral vein. Heparinization was administered for five days postoperatively. Convalescence after this was uneventful, save that she had considerable swelling of both thighs, which persisted for six weeks. In a late follow-up, I have learned that she is playing tennis, and, therefore, it is obvious that the swelling must have become greatly reduced.

CASE 6.—(See case report by R. S. Millen, this issue, p. 118.) At the first operation, I am sure that I had not sucked out the entire clot because I had not obtained adequate bleeding. The patient was extremely nervous, and it so happened that the tube supplied did not allow adequate suction for the removal of the thrombus. I have always felt that if I had been successful in the complete removal of her thrombus, the later sequelae might not have developed. When the thrombus developed in the right leg, I was confident that complete removal had not occurred, and the post mortem confirmed this observation.

CASE 7.—A young woman had a normal delivery, and, after her tenth post-operative day, developed a phlebothrombosis in her left femoral vein. The vein was exposed, the clot was sucked out, and free bleeding occurred. She went home a week after this procedure, and three weeks after she had been home, she developed phlebothrombosis of the right leg, and this clot was removed by another surgeon. Her convalescence in this case was uneventful.

Allen and his associates believe in the bilateral approach in all cases of phlebothrombosis. There is a certain amount of risk in the bilateral approach, because in sucking out the thrombus from one vein, one is likely to suck out more blood than one realizes, and bilateral approach might tend toward exsanguinating the patient. After analysis of the complications in general surgery and in obstetrics and gynecology, I am impressed with the fact that many of the thrombotic processes originate in the veins of the broad ligament, and that to successfully treat a gynecologic or obstetric case, if the patient will stand the procedure, a bilateral approach is the best procedure. Where the complication occurs as the result of some general surgical process, I believe that the treatment

in the pelvic veins at operation. Fifteen days later she was discharged with no apparent increase in size of the left leg. Some months following the operation a study revealed no increase in size of the left leg and full activity of the patient.

CASE 3.—Mrs. E. R. was operated upon at the North Country Community Hospital six weeks before term for a premature separation of the placenta. A living child was obtained and, after a normal postpartum course, the patient went home in good condition on her eleventh day. Two days later she began to feel a pain in her chest and was readmitted to the hospital with a suspicion of its cause being due to an embolus. However, examination revealed no evidence of any swelling in either leg, and the internist who had referred the case to me made a diagnosis of virus pneumonia, both by physical examination and x-ray studies. Daily investigation revealed no signs of phlebothrombosis until the tenth day of her readmission. That day Doctor Bancroft opened the left femoral vein under local anesthesia, due to the patient's pulmonary condition (since x-ray showed lesions in both lungs), and the patient's extreme nervousness and pleading against a general anesthetic. It was still thought that this patient's primary condition was virus pneumonia and that the phlebothrombosis was secondary to the enforced bed rest. Considerable pain and discomfort to the patient were encountered in this procedure and, although the clot was aspirated and a fairly good flow of blood was obtained, going over this case later by comparison with the other two cases operated upon, there was not the same vigorous back flow of venous blood. This patient was treated with intravenous and intramuscular heparin for one week, during which time no further chest symptoms were noted. Her temperature started to go down, and after several days she was allowed to sit out of bed, as it was felt that the virus pneumonia would not permit her temperature to go completely down and that it would be better for her to have a small amount of activity, rather than to keep her immobilized too long. The patient seemed to be improving, when suddenly she was again taken with an episode of pain in the chest, inability to breathe, etc. More râles were encountered in the chest on the right side where they had originally occurred. The left side by this time had cleared up to a marked degree. The patient was then kept in bed with some leg exercises. However, several days later swelling occurred in the right leg with tenderness over the right femoral vein. Doctor Bancroft operated this time under a spinal anesthesia which was given with particular care not to flex the thigh at the hip joint so as to in any way dislodge the clot. However, shortly before the patient was lifted from the stretcher to the operating room table she complained of a peculiar smell. It was felt that this might be largely due to the severe nervous strain that the patient was under and the operative procedure was carried out without any undue difficulty after 50 mg. of spinal anesthesia had been given. The operation was easily done and a very vigorous back flow was obtained. However, the patient's general condition was quite poor and she died thirty-six hours later. Postmortem examination revealed a complete obliteration of the right main pulmonary vessel and a partial obliteration of the left, so that she was only breathing with a small portion of the upper lobe of the left lung. The lesion in the left lower branch was old and well organized. That in the right contained an old and well-organized clot with a more recent one. This one probably occurred just before her second operation was done. There was definite involvement of the hypogastric veins, and there was no question but that the etiology of her chest condition all along had been emboli from a thrombophlebitis of the hypogastric veins, following her cesarean section.

I feel the failure in this case was not due to the surgical procedure, but perhaps to the selection of the anesthetic. Intravenous pentothal might have enabled

## ADVANTAGES OF SURGICAL TREATMENT IN PHLEBOTHROMBOSIS\*

ROBERT S. MILLEN, M.D., WESTBURY, N. Y.

*(From the North Country Community Hospital)*

I HAD occasion to see several cases within a short period of time in the fall of 1944 and was fortunate enough to have been able to obtain the help of Doctor F. W. Bancroft in the treatment of these patients. In view of the fact that he is presenting the paper of the evening on this subject, I will avoid any discussion of the anatomic approach to the operation, the advantages or disadvantages of the different types of heparin therapy, such as dicoumarol, intravenous heparin, or that given intramuscularly, and will merely state briefly the salient features in the case reports to illustrate the advantages of surgical treatment.

CASE 1.—Mrs. J. P. developed a femoral phlebothrombosis ten days after an easy, early, complete abortion at home. At the end of an afebrile week she was instructed to get out of bed, and active medical care was discontinued. However, she obtained a supply of seconal from a nurse friend and remained in bed. One week later she notified her family doctor that her leg had been swollen for several days. I was then informed of its occurrence and arranged for a consultation with Doctor Bancroft. A diagnosis of femoral phlebothrombosis was made, but, in view of the length of time since the onset of the swelling and the fact that the patient was at home, it was decided not to operate. She was kept in bed another eleven days. Eight days later, or twenty-six days after the onset, her leg was normal in size as long as her activity was limited to that necessary for minimal bathroom requirements. Some months ago, when examined, there was no swelling at all, even with exercise.

CASE 2.—Mrs. G. W. was delivered by another obstetrician at the Nassau Hospital. On her eighth postpartum day she began to have swelling of her left leg. Seven days later there was swelling of her right leg. The swelling started to go down six weeks later while she was still in the hospital. She was first seen by me eight and one-half weeks after the onset of her thrombophlebitis when there was still some swelling. She was turned over to Doctor Bancroft who advised continuance of the medical regime because of the long history. I understand that fourteen weeks later she was still having some pain and swelling in both legs on activity and was confined principally to her bedroom and bathroom.

The day following the consultation first mentioned, the same internist had Doctor Bancroft see another patient, Mrs. R. B., with phlebothrombosis, who had been under observation for menorrhagia at the North Country Community Hospital in Glen Cove for twelve days. The patient's left leg was definitely swollen, both in the thigh and in the calf. Doctor Bancroft removed an organized adherent clot from the left femoral vein, which vein was then cleared by suction with a cannula which was passed up to the bifurcation. The patient was also treated with heparin intravenously by a slow continuous drip for twenty-four hours, and during the following six days by intramuscular injections. She was out of bed in one week, and five days later a complete hysterectomy was performed by Doctor Corseaden of this Society. There was no sign of thrombi

\*Presented at a meeting of the New York Obstetrical Society, May 14, 1946.

I believe in giving dicoumarol on the third or fourth day following ligation. Whether that is beneficial or not I have not been able to determine.

DR. EDWARD G. WATERS.—Acute embolism that comes without warning is responsible for most of the deaths we encounter. We cannot do much about these at present; we cannot get to them quickly enough to ligate nor give the prophylactic treatment mentioned, with the possible exception of Dr. Bancroft's suggestion of thiosulfate. So we are limited to the case which gives warning, namely, the small embolism, and here we hope to prevent subsequent fatal embolism by one of the methods that we have available to us. The approach is by one of three methods which differ so much from the standard point of physiology that it is difficult to synchronize them. The first of these is a local surgical approach, the effect of which is obvious. The second is the method of blocking the preganglionic white rami communicantes of the spinal cord, thus producing dilatation, which may be achieved by spinal anesthesia, by paralumbar sympathetic block, or by high level caudal anesthesia reaching the tenth dorsal. The third is a purely medical approach by which we hope to prolong the bleeding time, check clot propagation, and prevent a fatal outcome when a small embolism has already occurred.

From different groups interested in the various approaches we get reports that are good, bad, and indifferent.

I think we have to go a long way yet before we finally get our bearings. What will the approach be to this subject ten years hence compared with that at the present time? The attitude now is to prevent the recurrence of an embolism when thrombosis is already present or preventing the extension of an endovascular thrombus.

At our clinic (Margaret Hague Maternity) we have not been using the operative approach. We have used caudal anesthesia, a great deal of sympathetic block, and more recently, dicoumarin.

I do not believe that, routinely, taking the prothrombin time in a patient with leg-calf tenderness is going to help very much. The readings are usually normal. In one recent case treated with dicoumarin for five days the prothrombin ratio dropped from 83 to 7 per cent. This may often occur, but is easily corrected by giving vitamin K and supplementing with whole blood transfusions if any hemorrhage occurs.

I would like to hear what Dr. Bancroft thinks the future approach to this particular problem may be. Admittedly, there are failures with the surgical approach. There are inadequacies in the method which blocks the sympathetic control of the peripheral vascular system, and we have not reached the end of our possibilities with anti-clotting medication.

DR. CHARLES M. McLANE.—Will Dr. Bancroft tell us what is the best treatment for the so-called fulminating type of phlebothrombosis which occurs in obstetric patients with an acute onset, rather high fever, and pain in the ankle advancing so fast that you can almost watch the pain ascend upward to the knee and thigh. Do you think such patients should be treated by ligation or should some of the medical methods be used, that is to say, whether caudal anesthesia, paravertebral block, or anticoagulins are better than ligation?

DR. RICHARD N. PIERSON.—I would ask whether oxytocics, particularly ergotrate, should be used sparingly because of their vasoconstricting effect.

I also would like to refer to the possible effects of tobacco. A patient with her first cesarean section developed a fairly severe thrombophlebitis for which she was given heparin for two weeks and recovered. She was an inveterate smoker, and the next time she became pregnant we persuaded her not to smoke, at least toward the end of her pregnancy. Her prothrombin times were normal post partum. She was out of bed on the third post-partum day and home on the eighteenth day. Five days later she phoned stating she had a pain in the leg. She started to smoke three days previously. Smoking could have been a factor in the condition.

a more thorough and less painful procedure and all the clot might have been removed. Also, by using hindsight it would have been wiser to have done both sides at the first operation.

The third case treated by surgery (Case 4) illustrates the advantage of the procedure to obstetric patients.

CASE 4.—Mrs. B. C., having been out of bed for several days, was discharged from the North Country Community Hospital on December 21, following a spontaneous primiparous delivery with a normal primiparous postpartum course, during which time she undertook frequent leg exercises. Slight swelling of the left leg was noted by the patient two days after discharge. This became marked the following day and I was called to see her at home. Examination revealed the typical tender swelling over the left superficial femoral vein, and the left calf was two inches greater in circumference than the right, and the left thigh one and one-eighth inches greater than the right. The patient was admitted to the hospital, and Doctor Bancroft removed the clot under intravenous pentothal anesthesia. Heparin was started and continued for one week. During the first twenty-four hours this was given intravenously. The rest of the time it was given on alternate days intramuscularly. In three days the left leg had gone down one-fourth of an inch in circumference. The patient was allowed out of bed on her third day, and discharged home at the end of the week to resume the care of her baby. At this time the thigh had gone down three-eighths of an inch and the calf three-fourths of an inch. Swelling persisted for some months. The amount of swelling was somewhat dependent on the amount of activity. When the patient was seen in June, 1945, the left thigh was one inch larger in circumference than the right, the left calf was three-fourths of an inch larger in circumference than the right, and she was symptom free.

### Discussion on Papers of Drs. Millen and Bancroft

DR. D. REES JENSEN (by invitation).—Thrombophlebitis or phlebothrombosis, the bland type, is a problem that besets also the general surgeon, and the question of what causes it is still unsolved. Many theories have been advanced, but none of them satisfies the conditions. Most of the patients have inflammation of the wall of the vein, and a thrombosis which is a concomitant manifestation of the disease. The question may well be asked: Why does Mrs. A. or Mr. A. get it and the next patient not get it?

I believe that, as heretofore conservative measures, such as treating this condition by elevation of the leg and long periods of rest in bed, do not satisfy the problem because it is uneconomic and the patient does not get well. In the immediate acute case treated by ligation, such as described, the result is usually excellent, and, while there are complications, they are minor in character.

We have treated a number of these cases at the New York Hospital and elsewhere which were in the acute stage, by which is meant the case occurs within a few days of surgical intervention. Conservative measures have not been satisfactory. When these patients get out of bed, they have large, swollen legs for a period of time; some of them have pain for many years; some of them eventuate into chronic ulcers; the patients must wear a support on the legs; they are never comfortable; they cannot work. I think ligation in the early case is indicated. Sulfadiazine and penicillin have been used without demonstrable benefit. There is the occasional case in which the clot breaks off in thrombectomy. That is not a criticism against the procedure for the reason that long, friable clots cannot be entirely aspirated from the external iliac and common femoral veins. It is amazing that more patients do not get them, but apparently they do not. The patient is allowed up (following thrombectomy) on the fourth, fifth, sixth, or seventh day, whereas ordinarily the patient is in bed for a long time.

distention and with distention there is compression of the vena cava with resultant venostasis.

Gentle handling of tissues is another factor in the reduction of emboli.

Insofar as the element of smoking is concerned, in the patient to whom Dr. Pierson referred, it must be remembered that in her case, the arteries were also affected, and often it is not just a venous condition; it is a combination of both. She had an absent dorsalis pedis and a very small posterior tibial pulsation, and it seemed that this might not be Buerger's disease, but something similar to it. Therefore, one has to consider tobacco and the spasm of tobacco as a factor in a good many of these conditions.

Dr. Waters has referred to some serious problems. I don't think I can answer them. The inflammatory type associated with periphlebitis, as evidenced by elevation of temperature, the sore, tender, and swollen leg, will be greatly benefited by lumbar block. In a series analyzed by Gallie of Toronto, only 10 per cent of emboli occurred in this group.

As for proximal ligation, some patients with phlebotrombosis and milk legs do not "shoot emboli" and get well, and that there is a fairly large group which "shoot emboli" and sometimes they are too big to do anything about, so if one goes into the surgery of vein ligation, one has to face the fact that one will perform a number of unnecessary operations.

I have used heparin for eight to ten days and found that, two days after stopping, the patients had shot emboli.

In answer to Dr. McLane, I assume he meant what I spoke of as the high temperature of acute phlebitis, what we used to call acute phlebitis and not the silent type, where the patient shoots an embolus. There I have not found that penicillin or any drug therapy has done much good. In cases in which we have excised veins we have never been able to grow cultures; why, I do not know. I think if I had a thrombus in my own leg, I would prefer ligation of the long saphenous vein rather than blocking of the lumbar ganglia. I feel that I would be less worried about it. I have seen one or two cases of novocain poisoning that were rather terrible to behold. They tell me that if barbiturates are given before the novocain, it diminishes the toxicity of the drug, so if we were to consider the occasional one who may be susceptible to novocain and give barbiturates, it may be of value.

To Dr. Millen, I would say I believe it is not only the flexion of the knees, but also the pressure on Poupert's ligament with a patient in the Gatch bed and tight abdominal dressings which may be a factor in venostasis.

DR. JOSHUA W. DAVIES.—As a prophylactic in the prevention of thrombophlebitis, I question the advisability of using anticoagulants in the antepartum period because of the bleeding which may occur during the third stage of labor. It is this part of labor which causes the obstetrician considerable anxiety, and to minimize the loss of blood, various oxytocics and even local anesthetics are utilized to facilitate the contraction of the uterus, which in turn lessens the amount of blood loss. After the completion of the third stage of labor, it might be of value to administer heparin or some anticoagulant in those patients who may be confined to bed for a longer period than usual, and particularly in those patients who are disinclined to early mobility.

I would like to ask Dr. Bancroft, why it is necessary to ligate the saphenous vein in addition to the ligation of the femoral vein. Ligation of the femoral vein would prevent the dislocation of the clot, but it seems to be the practice to ligate the saphenous vein also. Perhaps this procedure more effectively interrupts the sympathetic nerve supply to the superficial veins, and affords relief from pain by preventing vasospasm.

DR. BANCROFT (Closing).—I cannot answer all the questions that have been asked, but there are some interesting things in connection with a study of thrombosis and embolism. I have been working on this subject for quite a number of years. There was a time when we had a fund at the Fifth Avenue Hospital, and we did routine prothrombin and fibrinogen tests on all patients both pre- and postoperatively. I am very distinctly of the impression that there are potential "clotters" just as there are potential "bleeders." For example, we had one patient who rested her arm on a table and had a thrombosis of the median basilic vein.

The factors that we consider causes of thrombosis and embolism are trauma and infections and, most important, hemostasis. In our studies, we found that a certain number of patients have high prothrombin indices before operation, and that 14 per cent of all postoperative cases in our routine tests had high clotting factors, i.e., high prothrombin and fibrinogen. Of this 14 per cent, 2 per cent developed vascular accidents such as phlebothrombosis and thrombophlebitis. On analyzing the postoperative patients who were in the 14 per cent with high clotting factors, we found that they ran a longer elevation of temperature than is normal, and I feel confident that this group are the potential "clotters," and they may have had deep thrombosis which did not appear on the surface.

I believe that prothrombin is a very definite indicator and that it does not vary much. In other words, we have taken the normal as the denominator and the patient as the numerator, and found it was only about 0.8 per cent that puts a person in the bleeding diathesis and only 1.15 per cent that puts him in the clotting diathesis, and that it does not show a wide variation.

I believe that the high incidence of pulmonary accidents occurring in Sweden may have something to do with the high protein and fat diet prevalent there. The Smörgåsbord which is featured in most Swedish restaurants has a very high fat content.

Dr. Kosmak asked about hemorrhage. I think you can get hemorrhage from any anticoagulant. There have been hemorrhages reported from the mucous membranes and from wounds following the use of dicoumarol. I think that in the last report from the Mayo Clinic, more hemorrhages have been reported from the use of dicoumarol than from heparin. With heparin, its anticoagulant action ceases within two hours after its discontinuance.

Dr. Davies asked why, if we ligate the femoral vein, do we ligate the long saphenous vein? We don't always, but there are many patients with a process in both femoral and saphenous veins. I have had three patients in whom the femoral vein was exposed and it did not contain a clot, whereas when the long saphenous vein was investigated, it was found to contain a clot which extended into the femoral vein and extended up into the iliac. So if you are looking for a clot and it is not found in the femoral vein, you must look for it in the long saphenous.

Loose abdominal dressings, early feedings, and early evacuation of the bowels are important in the prevention of distention. A tight abdominal dressing is likely to create



investigators felt that if no diseased tissue were found, it was because of incomplete examination or due to the use of a microscope not sufficiently powerful to reveal the cause.

In the main, we may classify dysmenorrhea patients in one of two types: *primary* or *functional*, in which no pathology is found to account for symptoms; and, *secondary* or *organic*, in which is present some demonstrable local pathology capable of producing the symptom.

As science discovers more about dysmenorrhea, the functional nature of the disability becomes more and more apparent until at present many authorities hold that even chronic secondary dysmenorrhea has psychogenic factors in the background. If one considers case histories where painful cyclic symptoms appear (1) in congenital absence of the uterus, and (2) persist after removal of the uterus but not the ovaries, it becomes definitely certain that not all symptoms arise from the uterus itself.

### Evolution of Dysmenorrhea

Since all are familiar with the symptoms of functional dysmenorrhea, it is necessary only to review some of the contributory factors:

1. As a rule, the symptoms begin when the girl becomes sex conscious, rather suggestible, and more or less emotional.

2. There is a gradual increase in severity of the symptoms over a period of several years, the peak being reached between the ages of 18 to 20, with gradual subsidence due to normal changes of environment and interpersonal relationships.

3. Not all periods in the same individual are of the same severity. Emotional conflicts of any sort tend to exacerbate the pain, while agreeable social activities or praise from parent or employer have an opposite effect.

4. These symptoms are found in normal, healthy, ovulating girls and are usually cyclic, that is, they reappear at regular intervals.

5. Dysmenorrheics have a lowered threshold for pain, and this holds true even during the climacterium.

6. Some of the measurable physiologic changes of ovulatory menstruation are: (1) extracellular edema, (2) basal temperature changes, (3) muscle sensitivity (or tonic), (4) vascular changes,<sup>1</sup> (5) breast changes, (6) emotional changes, (7) genital changes.

### Symptomatology

All women who ovulate show these changes, although many deny their presence unless specifically requested to look for them. We find women who declare they have no warning of the onset of menstruation. When asked if they have pelvic discomfort, bladder frequency, engorged breasts, or a tingling feeling in the breasts, or headaches, they may or may not admit such feelings. Even if, upon direct questioning, they admit they feel tired, irritable or restless, depressed or unusually stimulated, or are conscious of fullness in the head, they insist they never let these symptoms interfere with their activities. Our patients universally admit emotional or nervous instability and one or more physical symptoms. In other words, women do have warnings of impending menstruation, if they look for and acknowledge them.



## THE PSYCHOSOMATIC ASPECT OF DYSMENORRHEA\*

### A Sensory Conditioning Process

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DYSMENORRHEA, in 1946, ranks as a major dysfunction among women of the Occident, and also among the educated classes of Oriental women. It is still spoken of as the "riddle of the ages." In the Ayur Veda, written 1,000 years B.C., there is mention of the pain of menstruation. It was Hippocrates who recommended cervical dilation as treatment for menstrual pain.

Today's increasing prevalence of dysmenorrhea may stem from the fact that modern mechanical inventions have relieved women of much drudgery, thereby giving them more time for introspection. The dissemination of modern medical knowledge has made the public conscious that minor disorders may lead to major catastrophes. The unfortunate angle of such propaganda is that minor disorders, when analyzed by the sufferer, and if dwelt upon, can easily lead to discomforts of major proportion.

The physiologist, the neurologist, and the psychiatrist tell us that the synthesis and analysis of stimuli that come from within and from without are functions of the cerebral cortex. From this hypothesis we hope to show that:

1. Dysmenorrhea for the most part is a normal sensory conditioned process that reaches abnormal levels.
2. That multiple inadequate sensory stimuli coming from several sources—of which pain is the dominant one—are effective in reaching threshold levels.
3. That repetitive, painful monthly stimuli above the threshold level increase the sensitivity to subsequent stimulation.
4. That psychic patterns are formed in the cortex.
5. That these phantom patterns are reversible.

To demonstrate the mechanism of increased sensibility we propose to point out some of the normal physiologic changes in the menstrual cycle that become exaggerated by a process of sensory conditioning and integration, and form psychic patterns in the cerebral cortex which produce pain and other disagreeable symptoms. We hope to show that these symptoms are not products of the imagination, but have a physiologic basis.

### Classification

Since dysmenorrhea is a symptom complex rather than a disease, it has been given numerous descriptive titles to fit the prevailing theories. The conception that all disease was based upon cellular pathology, as taught by Virchow, led to a fruitless search in the majority of cases of dysmenorrhea. For a time, in-

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is, that perception may be *either* aggravated or inhibited. It is *aggravated* by focussing the subject's attention on exciting stimuli, which may give rise to anticipatory states of anxiety or agitation such as may be manifested when a subject faces a dental appointment. It is *inhibited* when a subject participates in games of concentration or excitement, such as boxing matches or football games—sometimes to a point where *no* pain at all is felt.

In dysmenorrhea the question naturally arises, how do the normal moliminal symptoms following ovulation become exaggerated into the disagreeable disorders of which pain is the predominant symptom?

Wolff and Goodell,<sup>10, 11</sup> using a series of subjects, have shown that the pain threshold (perception) can be raised approximately 30 per cent for long periods by placebos; by distraction; and by suggestion or hypnosis. The success or failure of analgesics is markedly influenced by the confidence or lack of confidence the subject has in the efficacy of the drug (Figs. 1 and 2).

Haman<sup>12</sup> has shown that the dysmenorrheic individual has a relatively low pain threshold and is, therefore, more sensitive to all sensory stimuli.

Sensory conditioning is a stepped-up process of perception induced by repetition. It is a normal physiologic process of learning similar to that acquired in learning to appreciate, or depreciate, various types of music. To cite some examples of sensory conditioning in experimental psychology:

TABLE I. PAIN THRESHOLD IN FOUR GROUPS OF HUMAN SUBJECTS AS MEASURED BY THE SENSIMETER

GROUP	NO. OF CASES	AVERAGE PAIN THRESHOLD MEAN OF READINGS FROM RIGHT AND LEFT THUMB (SENSIMETER UNITS)
I. Dysmenorrheic	100	12.2
(a) Primary	50	11.4
(b) Secondary	50	12.9
II. Nondysmenorrheic	100	14.9
III. Postmenopausal	100	15.2
(a) Surgical	50	15.2
1. Had dysmenorrhea	25	14.7
2. Had no dysmenorrhea	25	15.6
(b) Physiologic	50	15.3
1. Had dysmenorrhea	25	14.4
2. Had no dysmenorrhea	25	16.2
IV. Male	100	14.6
All women	300	14.1
All subjects	400	14.2

Mowrer,<sup>13</sup> after a prolonged series of experiments, using gradually increasing painful stimuli, found that the subject often manifested an hallucinatory perception of pain; that is, felt pain when no stimulus was applied. For instance, applying an electrode to a subject's skin up to 200 times, he then instructed the subject to break the connection when again she should feel pain. At the 201st application the subject broke the connection, indicating pain was experienced, although actually the electrode had not been activated.

Ellson<sup>14</sup> by associating sound with light over a period of time, found that 80 per cent of his subjects reported hearing sounds when the light was shown and no sounds made.

Howells,<sup>15</sup> by associating a high tone with a green light and a low tone with a red light, after some 5,000 repetitions, found that his subjects continued to see the corresponding colors when the different tones were sounded, although

Exceptions are those females who do *not* ovulate at the beginning of the menarche, some in the reproductive cycle, and many approaching the menopause. "If she has dysmenorrhea she probably ovulates," is a precept in the medical profession. Other exceptions are cases of acute inflammation and cases where the pattern of pain has been well established.

### Etiology

There are as many alleged causes as there are women who suffer from this disorder. Each dysmenorrheic has her own idea concerning the cause, but few suspect the psychosomatic origin of the dysfunction in herself. Many doctors unconsciously find pathology to fit their preconceived ideas as to causes.<sup>2</sup>

It is important to bear in mind that dysmenorrhea occurs mostly in normal, healthy, ovulating women with no estrogen-progesterone imbalance, and whose bleeding is cyclic or regular<sup>3-6</sup> and accompanied by a secretory type of endometrium.

### Mechanisms Responsible for Pain Variations

The general theories regarding the mechanisms responsible for functional dysmenorrhea as we know it today are all based on some disturbance in the uterus either from:

1. Disordered myometrial contractility
2. Faulty endometrial separation or disintegration
3. Disturbance of the estrogen-progesterone balance
4. Chronic inflammation of visceral sympathetic connections.

There is no agreement among investigators that any single one of these factors is the cause of dysmenorrhea, except when pelvic inflammation is present.

It is significant that childbirth and age-increase tend to accentuate the pathologic changes in the musculature, the endometrium, and the arteries and nerves of the uterus, yet dysmenorrhea, when untreated, seems to diminish as these changes become more noticeable.

### What Is Pain?

Since *pain* is the aspect of the disease with which we are primarily concerned, it is necessary to understand something of the nature of pain and the mechanism by which it is raised to conscious levels. Lewis,<sup>7</sup> who has devoted years to the study of pain, says, "Pain cannot be defined, as it is something we *learn* from experience and *describe* by illustration." Main<sup>8</sup> says that the function of the sensory nerves is *to acquaint* the consciousness with the nature of the external and internal environment and regulate the autonomic processes.

### Mechanism of Sensory Conditioning

Walker<sup>9</sup> says there are three levels at which pain may be integrated: (1) the cortex, (2) the thalamus, (3) the tectum mesencephalon. He states that normal appreciation of pain occurs in the cerebral cortex. That at this level painful stimuli are modified by the activity of other cortical centers—that

the colors had been reversed. That is, the subject reported seeing the green color with the high tones, even though the red color was flashed, and vice versa.

Leuba,<sup>16</sup> using hypnosis to limit the subject's attention, states that "Our experiences indicate that after inadequate stimuli have been presented a number of times while the subject is experiencing certain sensations, the stimulus will of itself automatically and without intervention of any conscious process produce those sensations."

Through the demonstrations of these and many other investigators in experimental psychology we have come to believe that dysmenorrhea, the predominant symptom of which is pain, is one of the *sensory conditioning processes*.

Another, perhaps more familiar, is the intractable pain of phantom limbs, where the conditioning occurs through the repeated painful impulses arising from chronically irritated nerve endings before amputations.

Anderson and Parmenter<sup>17</sup> state that in animals emotional states may be induced by a feeling of uncertainty incident to the experimental procedure—a procedure involving a psychosomatic adjustment which the animal is forced to face and from which it cannot escape.

Most investigators agree that dysmenorrhea is associated with premenstrual tension which is the result of corpus luteum activity. To this we agree.

Weingraf<sup>18</sup> states that functional dysmenorrhea is an organ neurosis and gives the following reasons: (1) absence of pathology, (2) inconstancy of pain, (3) reversibility, (4) other neurotic stigmas, (5) amenability to a variety of treatments, (6) suppression by hypnosis.

We agree with these findings, but do not feel that the neurosis is psychodynamic as Weingraf says it is, or psychogenic as the textbooks describe it. We believe it is initiated and developed by physiologic changes rather than by suppression or repression of psychic episodes of the past. We admit that dysmenorrhea is far more common in nervous, emotional, impressionable women with inadequate personalities, but we find also that these same women have lowered pain thresholds and the condition definitely associated with corpus luteum activity.

Thus, by a normal process of sensory conditioning, a neurosis is developed and a patient's threshold for pain is further reduced.<sup>19</sup> We contend that the painful patterns are in the cerebral cortex. Proof of this is illustrated in the intractable pain of pelvic carcinoma that cannot be relieved by severing the viscerosympathetics, by rhizotomy, or by chordotomy.

Freeman and Watts,<sup>20</sup> by severing the nerve connections between the cortex and basal ganglion—lobotomy—relieve fear, anxiety, and emotional disturbances in psychopathic patients. They found that intractable pain not relieved by severing the afferent pain tracts could be relieved by *their* operation, which does not interfere with bodily activities. Van Wagenon of the Mayo Clinic by this operation has relieved the intense pain of a phantom limb after 13 preceding surgical procedures had failed. Rancy<sup>21</sup> and White,<sup>22</sup> have excised the cortical tissue where the pain patterns are found and relieved the pain of phantom limb.

We feel that psychic complexes in early adolescence are not necessarily the cause of dysmenorrhea, for we find many women without dysmenorrhea who

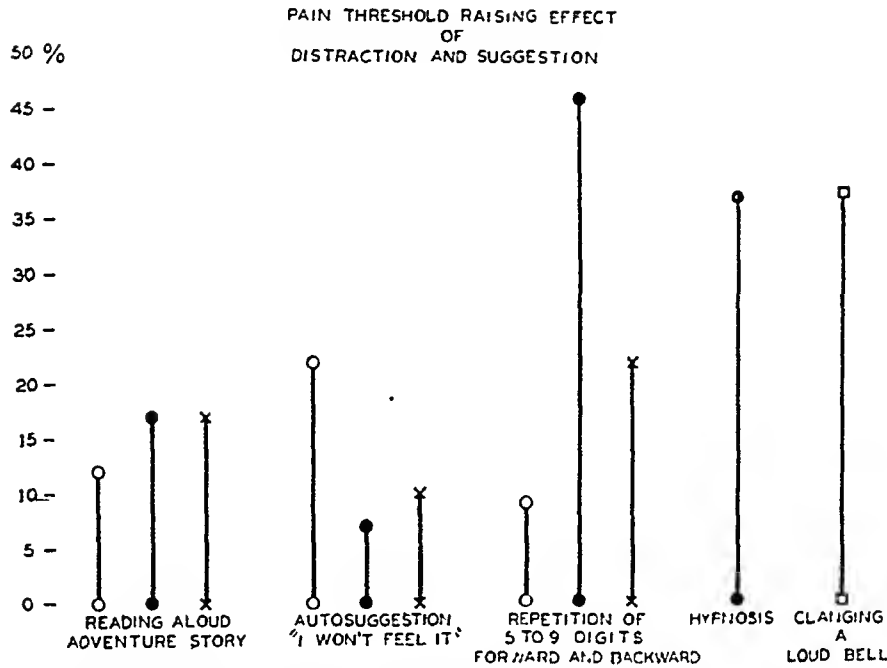


Fig. 1.—Chart showing the pain threshold raising effect of distraction and suggestion. The abscissa represents the “normal,” or control threshold for three individuals; the upper circles and crosses represent their thresholds raised by the various procedures. The per cent elevation of pain threshold above the control level is represented on the ordinate. (Reproduced by permission from the *Journal for Nervous and Mental Disease*, 23: 437, 1943.)

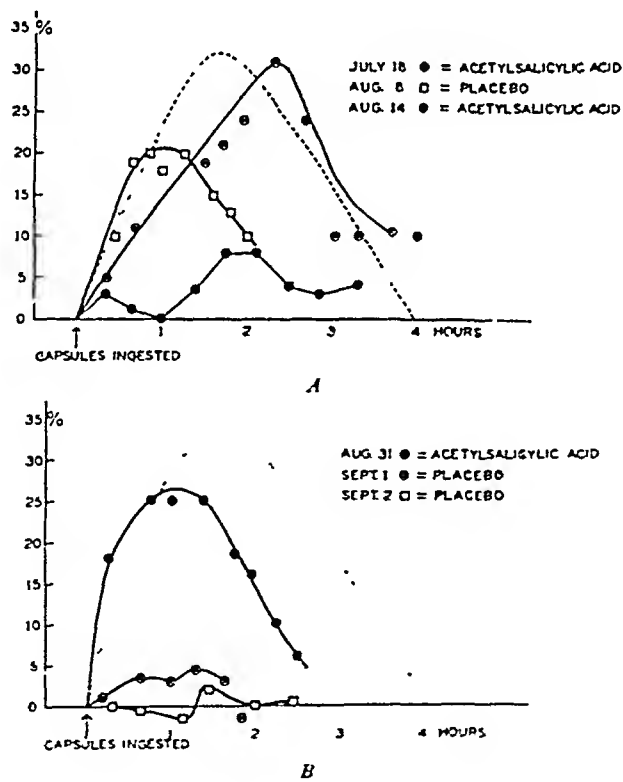


Fig. 2.—The effects of placebos and analgesics on the pain threshold of a suggestible woman. A, during a period of anxiety; B, during a period of assurance and relaxation. (Reproduced by permission from the *Journal for Nervous and Mental Disease*, 22: 439, 1942.)

dilatation of the cervix. While in this state she was impressed with the idea she would have no pain, and relief has been excellent for the past three periods. *Result*: Relief by narco-suggestion.

Numerous other patients including some with organic pathology have been relieved by hypnosis and by various injections and oral medication, accompanied by suggestion therapy.

CASE 4.—Mrs. W. O., aged 28 years, a college graduate who was known to be responsive to suggestion, was hypnotized and told that the normal symptoms associated with menstruation would be exaggerated and intensified during the following period. Definite symptoms of dysmenorrhea were induced that recalled milder attacks eight years previously. *Result*: Suggestive that dysmenorrhea is the result of physiologic changes. Probably simple reinstatement.

Résumé of Spaulding's case (Virginia M. Monthly 68: 105-107, 1941).<sup>23</sup>

Girl, aged 16 years, with cyclic episodes of headaches, general malaise, and severe drawing pains in both lower quadrants, but no bleeding. Uterus not felt by pelvic examination. Attempts to find and dilate the cervix were unsuccessful. Pains became more severe, necessitating confinement to bed for from one to three days. Laparotomy was decided upon. *Operative Findings*: Congenital absence of the uterus and one kidney. Normal functioning ovaries.

After operation, patient was relieved for three months, and then symptoms returned. Comment by Spaulding: "We firmly believed these pains were not of psychic origin, for the patient had pain for fifteen months before she had knowledge she was different from other girls."

### Discussion

We have given no new method of treatment, but have presented what we feel is the mechanism of much of the discomfort and suffering of dysmenorrhea.

It is generally agreed that corpus luteal activity produces physical changes such as temperature shifts, intracellular edema, muscle tonicity, breast changes, and vasomotor changes that lead to premenstrual tension and emotional instability. It is these changes that give rise to pelvic discomfort, bladder irritability, intestinal disorders, headache, fatigue, backache, and emotional upsets which are known as moliminal symptoms.

Most dysmenorrheics have been shown to have lowered pain thresholds, and are more susceptible to sensory stimuli than those with normal thresholds. By a sensory conditioning process these symptoms are exaggerated and the predominant symptoms may be expressed as migraine, painful breasts, or more often pelvic pain, since menstrual bleeding focusses the attention in the pelvis.

We have relieved cases by surgical and medical means. We have relieved an equal number by placebos and by suggestion, and also by suggestion under hypnosis. We believe that one method is as satisfactory as another, except where definite pathology is present.

We are told that the pain is an esthetic sensation that reaches consciousness in the cerebral cortex where its intensity is registered.

We believe that suggestion, either consciously or unconsciously, enters into the treatment of most cases of dysmenorrhea, since the percentage of cures as reported from either scientific or unscientific sources average about the same, except by castration or presacral neurectomy.

have had harrowing experiences in childhood and whose first menstruation was accompanied by psychic shock. The suppression of pain by hypnosis is no proof that dysmenorrhea is a psychogenic process, for it will relieve the pain of childbirth (by raising the pain threshold), or the extraction of a tooth just as readily. If, by psychoanalysis, the patient can be made to believe that the cause has been removed, the pain threshold is elevated and the symptoms relieved.

We have no quarrel with present methods of treatment of dysmenorrhea so long as they produce results without exploitation of the patient. We have found through experience that some dramatic procedure performed with confidence is necessary to relieve the average patient. To tell a patient bluntly that her condition is a psychoneurosis is most likely to be interpreted by her as an insult to her intelligence. Her natural reaction will be to seek another physician who, she may feel, has a clearer understanding of her suffering.

The following are brief summaries of a few cases temporarily relieved of some, if not all, of their disagreeable symptoms:

CASE 1.—Mrs. C. J., aged 38 years, requested a panhysterectomy. All previous treatment had given no relief. She had had no preconceived complexes in regard to menstruation. However, her first menstruation was marked by premenstrual tension. After eight hours of suffering and bleeding she revealed her embarrassing condition to her mother. With each succeeding period the girl's suffering grew worse until chills, syncope, and uncontrollable nausea and vomiting accompanied all periods. The usual home remedies and surgical dilatations of the cervix were tried with indifferent success. Marriage and pregnancy gave no relief. Presacral neurectomy was performed without relief. However, a succeeding pregnancy was accompanied by several episodes of painless contractions with bleeding, and was terminated in a precipitate delivery free of pain, demonstrating the sympathetic nerves had been interrupted. This was a marked contrast to her previous deliveries. With return of menstruation, the original intense dysmenorrhea symptoms reappeared, preceded each time by a week of nervous tension and anticipation, chills, syncope, nausea and vomiting, and bed for three days.

Through partial hypnosis by Dr. Dorcus her symptoms were greatly relieved for two periods, and the patient was able to carry on her household duties for the first time. Estrogen was then given to suppress ovulation, and the next period was so relieved she came to the office to report her appreciation. The next period was preceded by a painless diagnostic curettage, and secretory endometrium was found. This period was more painful. Restriction of sodium and the administration of chloride was tried and gave some relief at the following period. At present, the patient feels greatly relieved and will seek no further help if this status can be maintained. *Result:* Partial relief by hypnosis; definite relief by suppression of ovulation.

CASE 2.—Miss A. B., aged 21 years, the daughter of a Christian Scientist, was taught by her mother the normal physiology of menstruation. She had pain with her first period, followed by periods of increasing intensity. Pentothal sodium was given to dilate the cervix. While in this suggestible stage, she was told she would be free from dysmenorrhea, but would feel the usual minimal symptoms. *Result:* excellent.

CASE 3.—Mrs. L. C., aged 30 years, had dysmenorrhea with relief for four or five years following pregnancy. She was given sodium pentothal with feigned

## THE POSITIVE DIAGNOSIS OF HYDATIDIFORM MOLE WITHOUT EVIDENCE OF MOLE CYSTS

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**M**ANY textbooks state that mole is positively diagnosed by the passage of mole cysts. It is true that the evidence of mole cysts alone unaided by other data is enough to make the positive diagnosis of mole. Unfortunately, however, this does not always occur, and many cases of protracted bleeding are treated conservatively in the belief that one is dealing with threatened abortion. In a recent observation I noted that only 27.7 per cent of 137 cases were diagnosed as mole. The rest were mistaken for threatened abortion, fibroma, or placenta previa.

Careful history taking and physical examination are all that is needed in making the positive diagnosis.

When the uterus is larger than the corresponding size of pregnancy, one must consider the possibility of multiple pregnancy and hydramnios. In either of these cases fetal parts are palpable and, after the fifth month of pregnancy, fetal movements are felt by the mother. When such a group of data presents itself—uterine bleeding, especially if it be of dark chocolate color; the fundus uteri is very much higher than the corresponding period of amenorrhea; no fetal parts are palpable and no history of fetal movements, though the size of the uterus is that of six or more months of pregnancy; and failure to detect the presence of amniotic fluid in the uterus—mole should be highly suspected. With regard to the character of bleeding, one must remember that chocolate colored discharge may also be present in a pregnancy with a fetus, and that red blood may also be present in mole.

Though in the majority of cases of mole the uterus is larger than the corresponding period of amenorrhea, in a few the uterus is not larger and may even be smaller than that of a normal pregnancy, and in some cases no menstruation appears after the last pregnancy so that one cannot relate the age of amenorrhea with the height of the fundus. When the condition is hydatidiform mole, vaginal examination will show that part or the whole of the lower uterine segment is full, due to its soft molar contents. Careful bimanual examination will show that no fetal parts can be appreciated.

The feeling of the fullness of the lower uterine segment as if occupied by soft tissue in conjunction with the preceding data has enabled the writer to diagnose positively the last consecutive cases of hydatidiform mole.

In mole, moreover, where the uterus is of the size of a five months' pregnancy, the uterine sound by gentle introduction into the uterine cavity reaches far beyond the lower segment. This does not happen in a normal five months' pregnancy where the sound becomes arrested by the membranes beyond the cervix. Special precaution should be observed when employing this method. It should be done with the utmost gentleness and under the greatest aseptic precautions in the delivery room or operating room where dilatation and curettage may be immediately done if necessary. For, sometimes, with the introduction of the sound, bleeding may ensue which can be stopped only by the immediate evacuation of the uterus.

I now seldom resort to this method for the history of amenorrhea and of absence of fetal movements, the fullness of part or the whole of the lower uterine



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uterine segment. She was immediately curetted, and many mole cysts of the large and fine variety, especially the latter, in addition to placenta-like tissue was evacuated.

CASE 5.—F. P., 28 years of age, gravida ii, was admitted to the Philippine General Hospital on Feb. 2, 1944, because of bleeding after three months of amenorrhea. The fundus uteri was one finger below the umbilicus, no fetal parts could be palpated, nor could amniotic fluid be detected, and there was fullness of the lower uterine segment. She was immediately curetted, and numerous fine and large mole cysts were evacuated. Early microscopy showed undue activity of the trophoblasts; but, in view of her youth and her desire for another child, she was allowed to go home with the instruction to return to the hospital in case she should bleed. She bled twice—on the thirteenth and on the twenty-fifth day after the curettage. The diagnosis of uterine chorionepithelioma by my method was made, and on Feb. 29, 1944, or twenty-six days after the curettage, a supravaginal hysterectomy and double salpingectomy were done. Section of the uterus showed button-size growth of chorioepithelioma, having a diameter of 1.5 cm. on the upper posterior wall.

### Conclusion

A method of diagnosing hydatidiform mole positively is presented which consists of (1) the fullness of part or the whole lower uterine segment in conjunction with (2) undue uterine enlargement as related to the number of months of amenorrhea, (3) uterine bleeding, (4) absence of fetus as revealed by palpation auscultation and of fetal movements, and (5) absence of amniotic fluid.

segment, in addition to the bleeding undue uterine enlargement as related to the months of amenorrhea, and absence of the fetus and of the amniotic fluid constitute the positive diagnosis of hydatidiform mole. One must rule out, of course, uterine fibroid, especially when the tumor is intramural and especially if it affects only a part of the wall including the lower segment, for such a condition gives rise also to a deep uterine cavity and bleeding. But then, in such a case the uterine cavity is empty and there is usually no amenorrhea.

The following case reports are explanatory of the method.

### Case Reports

CASE 1.—P. S. L., aged 24 years, gravida ii, was admitted to the Philippine General Hospital on Sept. 30, 1944, as a case of threatened miscarriage. She had aborted at home in May, 1943, and she had had normal menstruation in July and August. Since the latter part of September and October she had scanty bleeding off and on. On admission, she had edema of the feet and legs; her blood pressure was 170/84. I was called to see the patient on October 24. The elongated pear-shaped uterus had its fundus one finger below the umbilicus. No fetal parts could be palpated, nor could amniotic fluid be detected. There was no history of fetal movements, nor could they be appreciated. Internal examination showed a small closed cervix without bleeding. But the posterior lower segment was felt to be bulging. The uterine sound could be gently introduced upward unobstructed. The diagnosis of hydatidiform mole was made and the uterus was immediately emptied of the mole cysts.

CASE 2.—L. A., aged 22 years, gravida ii, was admitted on Oct. 2, 1943, with the complaint of dark bloody discharge which had been appearing off and on since one month ago, but which had been continuous for the last fifteen days. Her first pregnancy ended in a full-term spontaneous delivery in September, 1942. She menstruated only once after delivery in December, 1942. She noticed gradual enlargement of her abdomen since June, 1943. On admission, the fundus uteri was one finger below the umbilicus. No amniotic fluid could be appreciated and no fetal parts could be felt. Internal examination showed fullness of the anterior lower segment. No resistance was met by the uterine sound introduced high up into the uterine cavity.

The positive diagnosis of hydatidiform mole was verified by the immediate curettage.

CASE 3.—P. C., 24 years of age, gravida ii, was admitted to the Philippine General Hospital on Oct. 1, 1943, as a case of threatened miscarriage. Her first pregnancy ended in a three months' abortion in May, 1943. She menstruated in June but not in July and August, and on September 29 she began to have slight bleeding. I was called to examine her on October 4, and the findings were: the uterus was enlarged as if five and one-half months pregnant, the fundus being just below the umbilicus. No fetal parts could be felt, nor could amniotic fluid be appreciated. Internally there was fullness of the posterior lower segment. The uterine sound could be introduced high up into the uterine cavity without resistance. Immediate curettage revealed small molar cysts with some admixture of placenta.

CASE 4.—C. D., aged 24 years, gravida iii, was admitted on Aug. 10, 1943, with the diagnosis of threatened miscarriage. Her first two pregnancies had ended in full-term deliveries. She complained of bleeding for the last fifteen days. The bleeding began three months and fifteen days after her last menstruation. On abdominal examination, the fundus uteri was one finger below the umbilicus, and no ballottement of fetal parts could be elicited. Internal examination showed the cervix to be closed, and there was fullness of the lower

TABLE I. REPORTED CASES OF CARCINOMA OF THE CERVIX IN PATIENTS 20 YEARS OF AGE AND YOUNGER

NO.	AUTHOR	YEAR	HISTOLOGY	AGE	REMARKS	5-YEAR SURVIVAL
1.	Schauta	1880	Carcinoma (malignant adenoma)	17 yrs.	Died of cancer within 7 months	No
2.	Eckardt (on Fraenkel's)	1887	Carcinoma, called sarcoma at first	19 yrs.	Probably from glands of the cervix	No
3.	Ganghofer	1888	Medullary adenocarcinoma	8 yrs.	Died of intercurrent variola	No
4.	Tschop	1897	Carcinoma, type not mentioned	19 yrs.	Believed to have been cured. No follow-up	Yes
5.	Boyd	1905	Papillary adenocarcinoma in part; other areas like endothelioma	18 yrs.	Without disease 1 year	?
6.	Philipp (on Pfaundler's)	1907	Adenocarcinoma first, then changed to endothelioma	3 yrs., 3 mos.	Passed pieces of tumor per vaginam which were adenocarcinoma on section	No
7.	Glöckner	1908	Adenocarcinoma	7 yrs.	Died of cancer, 4 years	No
8.	Bumm	1909	Adenocarcinoma	7 mos.	Died in 8 weeks. May have started in vaginal mucosa next to cervix	No
9.	DeRouville	1912	Epithelioma	18 yrs.	No recurrence 10 months after radical panhysterectomy	?
10.	Cragin	1913	Carcinoma, type not mentioned	18 yrs.	Without disease 5 months after radical panhysterectomy	?
11.	Wells	1913	Adenocarcinoma	18 yrs.	No evidence of disease, 4 years. Radical vaginal hysterectomy	?
12.	Adams	1915	Adenocarcinoma at first, then changed to teratoma	2 yrs., 6 mos.	Entire cervix and fundus were involved	No
13.	Darnall	1920	Adenocarcinoma	20 yrs.	Died postoperatively; pulmonary embolus	No
14.	Findley (on Franz's)	1924	Adenocarcinoma	6 mos.	Seen in Franz's clinic. Died of cancer in 10 days	No
15.	Aguinaga	1925	Carcinoma, type not mentioned	14 yrs.	Cautery and radium. No recurrence at 13 months	?
16.	Heusinkveld	1925	Adenocarcinoma	20 yrs.	Without disease 4½ yrs. Died of cancer 5½ years	Yes

## CARCINOMA OF THE CERVIX DURING THE FIRST TWO DECADES OF LIFE

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THE apparent tendency of cancer to manifest itself to an increasing degree during the earlier decades<sup>7</sup> is a fact calling for more emphasis in current medical literature. It should be evident that no age barrier exists excluding the presence of "adult" lesions in young people.

We have been taught for so many years that cancer of the uterus always occurs about the time of the menopause, that unless one is alive to the fact that it can occur at any age, an early case in young women will be overlooked.<sup>6</sup>

Scheffey, Farell, and Hahn<sup>22</sup> note that 27 per cent of the patients with cancer of the cervix seen at the Jefferson Medical College Hospital were below 40 years of age. Hall and Bagby<sup>7</sup> state that 7.4 per cent of the patients with cervical cancer seen at the Barnard Free Skin and Cancer Hospital between 1933 and 1938 were below 30 years of age. Gibson<sup>6</sup> notes that 9.9 per cent of his series of uterine cancers were in women below 30 years. Petersen<sup>18</sup> states, after a review of 500 cases, that uterine cancer in general occurs in an appreciable percentage of cases between 20 and 25 years of age, 4.8 per cent of his cases occurring between 20 and 30 years of age.

Yet, despite the not infrequent occurrence of uterine cancer in young women, its presence in those below 20 years must be classed as exceedingly rare.

Koblanek<sup>11</sup> found only two under the age of 20 years after reviewing 6,354 cases. McGlinn<sup>14</sup> studied 2,291 cases and noted only 0.5 of 1 per cent under the age of 24 years. Paek and LeFevre<sup>17</sup> reviewed 2,134 cases of uterine cancer seen at Memorial Hospital between 1917 and 1929 and found only two within this age group. A review by Bowing and McCullough<sup>1</sup> of 3,000 cases of cervical cancer seen at The Mayo Clinic revealed only one below 20 years of age. Because of its rarity in these years, the diagnosis of uterine cancer is often confused or missed entirely.

### Analysis of Thirty Cases Collected From the Literature

A diligent survey of the literature reveals thirty cases of true carcinoma of the cervix which occurred during the first two decades; these are listed chronologically in Table I. We are adding the thirty-first. Only those cases of histologically proved carcinoma of the cervix have been tabulated. The sarcomas and teratomas have not been included. Undoubtedly, more cases of cervical carcinoma than are listed here have occurred,<sup>20, 25</sup> but in those instances information was not complete enough for tabulation or the case was unavoidably missed.

Bowing and McCullough<sup>1</sup> reviewed the literature in 1941 and found only eleven proved and classified cases of cervical carcinoma below 20 years. They added a twelfth. Morehead<sup>15</sup> in 1944 found seventeen cases of histologically proved cervical carcinoma in patients 20 years of age and younger.

The youngest case, 6 months old, was seen in Franz's clinic in Berlin. Findley<sup>2</sup> examined the specimen and made note of the extraordinary age.

It is of interest to note that the overwhelming majority of these patients had an adenocarcinoma. This type of histology seems to prevail among groups of younger patients with cervical cancer, although Pack and LeFevre<sup>17</sup> state that the average age of patients with adenocarcinoma of the cervix is the same as for those with epidermoid carcinoma. Petersen,<sup>18</sup> however, states that in his series the age group was lower in those patients with adenocarcinoma.

This form of carcinoma in itself, when found in the cervix, is a relatively rare lesion. In Pack and LeFevre's<sup>17</sup> series, only 0.42 per cent of all cervical cancers were of this type. Healy and Twombly<sup>8</sup> found 1.9 per cent in their cases, but in Petersen's<sup>18</sup> material, 9.1 per cent of the cervical cancers were adenocarcinomas. Of the patients listed in Table I, 22, or 70.9 per cent, had this type of histology. Only four (12.9 per cent) had squamous lesions, and four were not classified. The cancer of one patient had both squamous and glandular features.

There were only four patients in the collected series that survived five years. Of these four, the cure in one is of questionable authenticity and one died of cancer shortly after passing her fifth year following treatment. The two remaining cases are five-year cures. Both of these were treated by cauterization of the cervix, and then radium in the form of a cervical applicator. One (Ludwig<sup>13</sup>) also received x-ray treatments.

Six patients were free from cancer for periods ranging from five months to twenty-eight months after treatment was instituted, but further follow-up information on these cases is not available. One case (Wells<sup>25</sup>) was free from cancer four years after treatment; one died three and one-fourth years after treatment; and two others died in the fourth year following therapy. With these exceptions, all died within a short period after beginning treatment or establishment of a diagnosis. Growth and spread of the lesion is very rapid, therefore it would seem that only when treatment is instituted early can any hope of cure be entertained.

### Case Report

M. M., an 18-year-old, American born, unmarried woman, gravida 0, of Italian heritage, was first seen in the examining office of Memorial Hospital on June 16, 1945. She had been complaining of irregular and heavy vaginal bleeding for the previous two years. She started to menstruate at the age of 15 years, menses occurred regularly every thirty days and lasted for five days. They were not painful and appeared normal in all respects. At the age of 16 years she noted the onset of irregular vaginal bleeding. Mild spotting followed her usual menstrual flow, which spotting soon turned to the passage of large clots of blood and debris lasting four to five days at a time, and then suddenly ceasing. At times she would be free of irregular bleeding for two or three months, but it would eventually recur.

TABLE I—CONT'D

NO.	AUTHOR	YEAR	HISTOLOGY	AGE	REMARKS	5-YEAR SURVIVAL
17.	Lisa and Cornwall	1926	Squamous carcinoma	16 yrs.	Died within 5 months	No
18.	Bonner	1927	Adenocarcinoma	13 yrs.	Without disease 19 months. Caustery removal cervix and radon seeds	?
19.	MacDonald	1929	Adenocarcinoma	10 yrs.	No follow-up	?
20.	Morse	1930	Adenocarcinoma	10 yrs.	Died of cancer, 1 year. Inoperable. May have come from fetal rests in pelvic cavity (Ewing)	No
21.	Pack and LeFevre	1930	Adenocarcinoma	20 yrs.	Probably from embryonal rests. Died of cancer 4 years	No
22.	Amesse	1932	Adenocarcinoma	24 mos.	Questionable whether origin in cervix or fundus	No
23.	Scheffey and Crawford	1932	Adenocarcinoma	22 mos.	Died of cancer in 7 weeks	No
24.	Glass	1933	Partly adenocarcinoma and partly squamous carcinoma	16 yrs.	Died of cancer, 3 years, 3 months	No
25.	Lockhart	1935	Adenocarcinoma, papillary type	2 yrs., 3 mos.	Symptoms began at age of 14 months	No
26.	Ludwig	1936	Adenocarcinoma	16 yrs.	No evidence of cancer, 5 years. D & C with caustery removal of cervix. Radium (3,160 mg. hrs.) and x-ray	Yes
27.	Bowing and McCullough	1941	Adenocarcinoma	13 yrs.	Alive and well 6 years. Cauterization of cervix with 676 mg. hrs. cervix applicator	Yes
28.	Shaw	1941	Adenocarcinoma	15 yrs.	Died within 8 months	No
29.	Morehead	1944	Squamous carcinoma	19 yrs.	Died of cancer 3 months	No
30.	Morehead	1944	Squamous carcinoma	20 yrs.	No evidence of cancer, 2 years, 4 months. Radium	
31.	Taylor and Pollack	1946	Adenocarcinoma	18 yrs.	Alive with cancer, 9 months. Inoperable. Radium and x-ray	

250 kilovolt unit where she received 1,750 r. further for a total of 2,500 r. through each portal.\* Treatment was given through two ports daily, and lasted approximately six weeks, at which time the tumor was definitely movable, even in the left parametrium, and an attempt at radical panhysterectomy was decided upon. The skin reaction was moderate. On cystoscopy the bladder was normal throughout and No. 7 French ureteral catheters were passed easily to each kidney pelvis.

The patient had a laparotomy on Sept. 11, 1945. The fundus was anteverted, small, and freely movable. The adnexa were unremarkable, and there were no hypogastric nodes of significance. The parametria were invaded, especially on the left. The cervix was replaced by a large, hard, fungating mass which invaded the base of the bladder on the left side. A biopsy taken at this point during the operation was reported as "malignant tumor" on frozen section. Because of this, the case was considered inoperable and the abdomen was closed. Her postoperative course was uneventful. The wound healed well.

On Sept. 21, 1945, 3,000 milligram hours of radium in the form of a cervical applicator was inserted, and, on September 24, an additional 1,500 milligram hours was given to the cervix and parametria in the form of a vaginal bomb. She was then discharged to the outpatient department, and on October 15 received 500 milligram hours more with a small vaginal bomb.

Three months later, although she looked and felt considerably better, there was still induration and thickening in the parametria with a small crater on the left side indicative of both residual cancer and radiation necrosis. A large mass was felt in the region of both uterosacral ligaments, and probably represented more residual disease. There was marked radiation tanning of the skin of the abdomen and back. Further treatment could not be tolerated. When last seen, nine months following her initial visit to the hospital, she complained of slight bleeding from both the rectum and vagina with mild generalized abdominal cramps and urinary frequency. The mass had increased in size and was causing partial obstruction of the rectum.

### Comment

The history and course of this patient are similar to other patients in the group under study. Oftentimes the first vaginal examination reveals a large, bulky tumor presenting at the cervical canal and in such a manner as to make the exact site of origin uncertain. The addition also of a foul odor with profuse bleeding, and in some cases the passage of bits of tissue, is another common feature.<sup>16, 19, 21</sup> Growth of the tumor and its metastases appeared to be very rapid. Gibson<sup>6</sup> states that unless these patients are seen within the first three months of disease, a radical operation cannot be done. The fairly quick downhill course seen in this case, despite the application of radium and x-ray to the limit of tolerance, was the usual picture in the majority of others.

It is of little advantage to speculate on the role played by the endocrine preparation given to this patient. Geist and Salmon<sup>4</sup> could find no evidence of abnormal proliferation in the endometrial or vaginal mucosa of 206 patients who had been treated with huge doses of estrogens over periods of time extending to five and one-half years. Nevertheless, that estrogens are possibly carcinogenic under certain circumstances and may play a role in the genesis

\*The 1,000 kilovolt unit broke down and, rather than wait for its repair, treatment was immediately changed to the 250 kilovolt machine.



The patient consulted her local physician shortly after the onset of her irregular hemorrhages. A dilatation and curettage was immediately advised, but refused by the patient because of her virginity. She was therefore given "two injections of testosterone propionate, 0.025 Gm., about three weeks apart with no cessation of the bleeding. She was then given a prescription for 0.005 Gm. of stilbestrol which she was instructed to take every four hours until the bleeding stopped or the drug was used up." On this regime, her bleeding lessened and did stop, only to begin again within a short period. As soon as the bleeding started, she resumed taking stilbestrol. It is estimated that she took this medication, off and on, for two years.

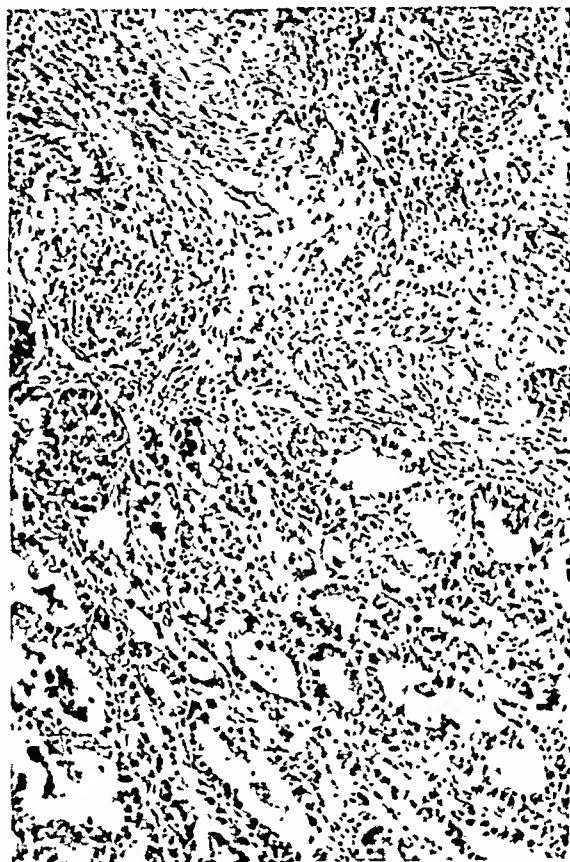


Fig. 1.—Microphotograph of biopsy taken when the patient was first examined at Memorial Hospital.

In January, 1945, the bleeding and discharge became more profuse, of longer duration, and very foul smelling. Her local physician continually advised a uterine curettage but the patient constantly refused. The bleeding became so severe by June, 1945, that a dilatation and curettage was finally permitted. Pathologic report of the curettings was adenocarcinoma, grade III, and the patient was referred to this hospital.

Physical examination was not unusual with the exception of the uterus. The fundus felt normal in size, was forward and freely movable. The adnexa were not felt. The cervix was replaced by a huge fungating tumor the full extent of which could not be made out through the nulliparous vaginal introitus. The parametria were thickened and indurated on both sides with fixation on the left. Biopsy of the tumor was taken and proved to be adenocarcinoma, grade III (Fig. 1).

Treatment was started with the million volt x-ray unit: she received 750 r. to each of six external lower abdominal ports, and then was changed to the

## ACUTE LEUCEMIA AND PREGNANCY

### Report of Fatal Case Treated With Penicillin

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THE relatively rare combination of pregnancy and acute myelogenous leucemia in which the effect of penicillin was studied warrants the reporting of this case.

*First Admission.*—M. W., a pregnant white housewife, aged 34 years, entered the medical service of the Metropolitan Hospital on March 3, 1945, with a marked sore throat and difficulty in swallowing of four days' duration. Two weeks before admission she noted headache, backache, malaise, weakness, and a temperature of 101° F. One week later she felt well enough to resume her household duties. Four days before admission the same symptoms returned and her temperature rose to 103° F. When her condition persisted unchanged after a brief course of sulfonamide therapy, the patient was taken to a private hospital where her blood picture was found to be that of an acute myelogenous leucemia. Since her condition remained critical, she was transferred to the Metropolitan Hospital where the diagnosis of acute myelogenous leucemia was confirmed.

Past history revealed that prior to the onset of her present illness on Feb. 14, 1945, she was in excellent health, except that she bruised easily. Unfortunately, no blood examination was done at any time before her present illness. Her first pregnancy ten years ago was uncomplicated, and her only child, a boy in good health, was found to have a normal blood picture. Menstrual history was essentially normal. She was five months pregnant on admission, her last menstrual period having occurred on Sept. 24, 1944.

The family history was essentially noncontributory.

On admission, her temperature was 101° F., pulse 100, and blood pressure 115/60. Physical examination revealed a moderately obese, pregnant woman who appeared markedly pale, toxic, and weak. She was in respiratory distress due to her swollen, edematous pharynx which was also painful and ulcerated. Both tonsils were enlarged and covered with mucus. On the left anterior tonsillar pillar there was a superficial ulceration, bleeding easily on touch. The gums were congested; the right side of the neck was more swollen and tender than the left. Both eyes were suffused. Examination of the ears and nose was noncontributory. There were enlarged, firm, tender cervical lymph nodes and small inguinal nodes.

Examination of the heart and lungs was negative. The breasts were enlarged. The liver and spleen were not palpable on admission nor at any subsequent time. The uterus extended to one finger below the umbilicus. Fetal movements and heart sounds were present.

The peripheral blood picture on admission was as follows: erythrocytes, 2.10 million; leucocytes, 90,000; differential count, 70 per cent myeloblasts, 10 per cent promyelocytes, 10 per cent polymorphonuclear neutrophils, and 10 per cent lymphocytes (Fig. 1). Rare normoblasts were noted. The bone marrow examination revealed a markedly hyperplastic marrow with severe reduction of the erythroid elements (Fig. 2). There were 47 per cent myeloblasts, 28 per cent promyelocytes, 10 per cent neutrophilic myelocytes, 1 per cent metamyelo-

of uterine cancer has been the subject of much clinical and laboratory research.<sup>3, 5, 9, 10, 12, 22, 24</sup> Because this possibility, no matter how remote, is fraught with such serious implications, it should at all times be considered.

However, in this particular case, the exact amount of estrogens taken is unknown, and certainly, we cannot say that the patient did not have cancer at the very start of her symptoms before any medication had been taken. The important lesson to be learned is that indiscriminate use of endocrine therapy for the control of abnormal uterine bleeding often masks an underlying organic cause. Endocrine preparations of various sorts are being increasingly used to administer "cures" when the disease itself not infrequently is cancer. Because of this practice, the diagnosis of uterine cancer is often delayed. Scheffey and his co-workers<sup>22</sup> have recently reported a series of cases of uterine cancer referred to them in which the correct diagnosis was long withheld because of the administration of endocrine preparations, thus lulling both patient and doctor into a false sense of security and dampening the ultimate prognosis.

### Summary

Thirty patients, 20 years and younger, with true carcinoma of the cervix were reviewed from the literature. A similar lesion in a young woman of 18 years was presented by us. The histologic type in 22 patients was adenocarcinoma. In the majority the clinical course was progressively downward. Four patients survived five years.

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In view of the preceding findings, it was believed that the patient suffered from an acute myelogenous leucemia presenting throat lesions and aggravated by secondary infection. Because of this the patient received 10,000 Oxford units of penicillin intramuscularly every three hours after two initial doses of 20,000 and 15,000 units. Oxygen was given and frequent throat irrigations, as well as mouth washes with equal mixtures of hydrogen peroxide and water, were initiated. Under this therapeutic regime the clinical condition of the patient improved rapidly, and her temperature dropped to normal (Fig. 3). Despite this clinical improvement, however, her blood picture continued to show the presence of a high percentage of myeloblasts and other early forms (Table I).

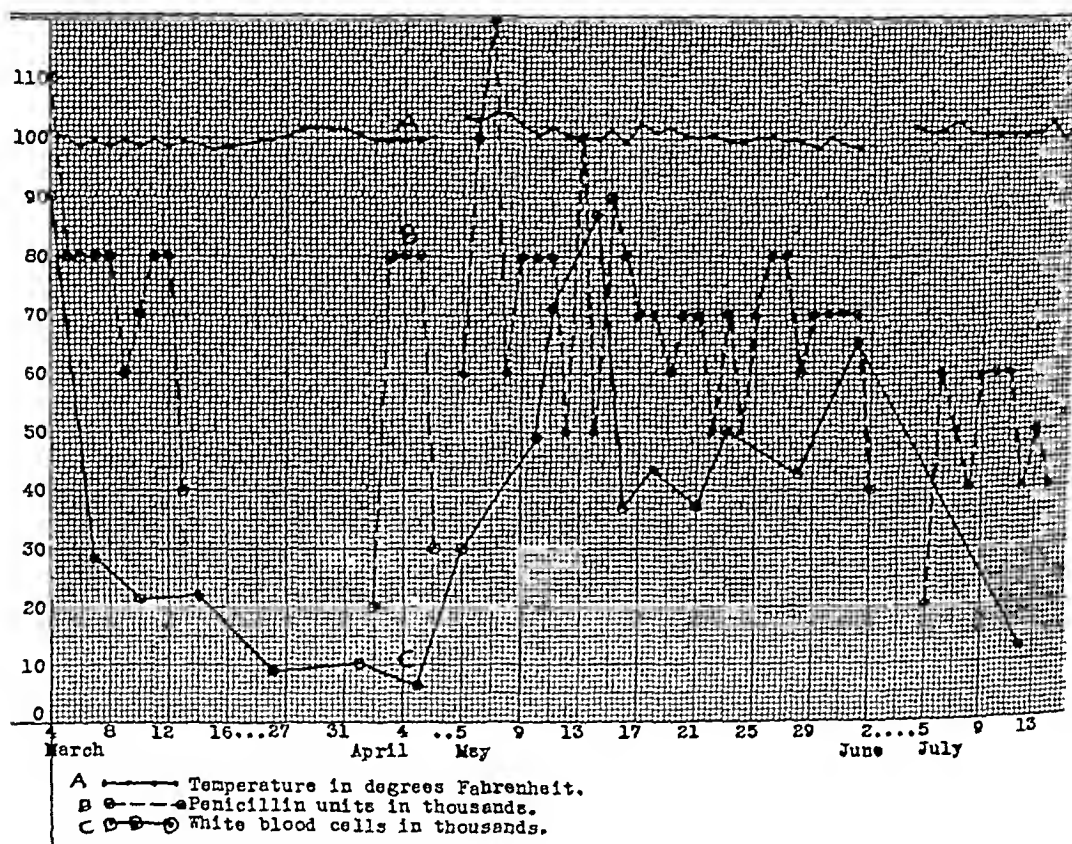


Fig. 3.—Graph demonstrating the relationship of temperature and white blood cell count to total daily penicillin dosage.

Six days after admission the patient started to stain vaginally, but had no labor pains. A transfusion of 250 c.c. of type A blood was given to relieve the patient's anemia. Half an hour after the conclusion of this transfusion the patient experienced a reaction with severe chills, rapid pulse, and a rise in temperature. The next morning the patient aborted without any postpartum complications.

Several hours after the miscarriage, an autopsy was performed on the five months' female fetus without disclosing any gross abnormalities. Histologic examination demonstrated no leucemic infiltration in the tissues, placenta, and membranes. Peripheral blood and bone marrow smears made at autopsy showed no evidence of leucemia in the stillborn.

Despite her marked anemia and abnormal blood picture, the patient continued to feel well until March 26 when she broke out into a generalized urticarial eruption for which no etiology could be determined. At this time she was receiving only iron and vitamin preparations in addition to her regular diet.

cytes, 3 per cent stab neutrophils, 7 per cent segmented neutrophils, 3 per cent lymphocytes, 1 per cent eosinophils, rare megakaryocytes, and five normoblasts per 100 white blood cells. The granulocytes gave a positive peroxidase reaction.

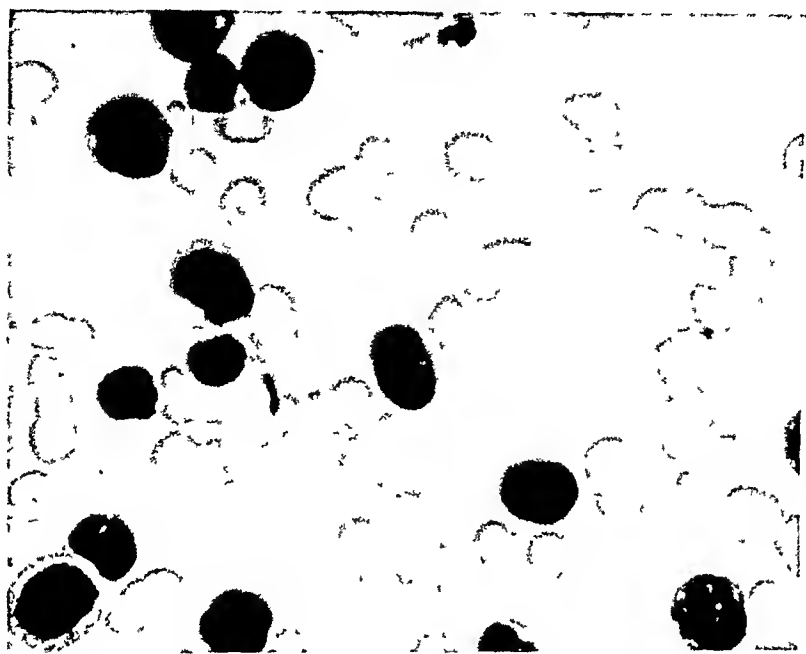


Fig. 1.—Peripheral blood smear of mother on admission showing presence of myeloblasts and promyelocytes (oil immersion).

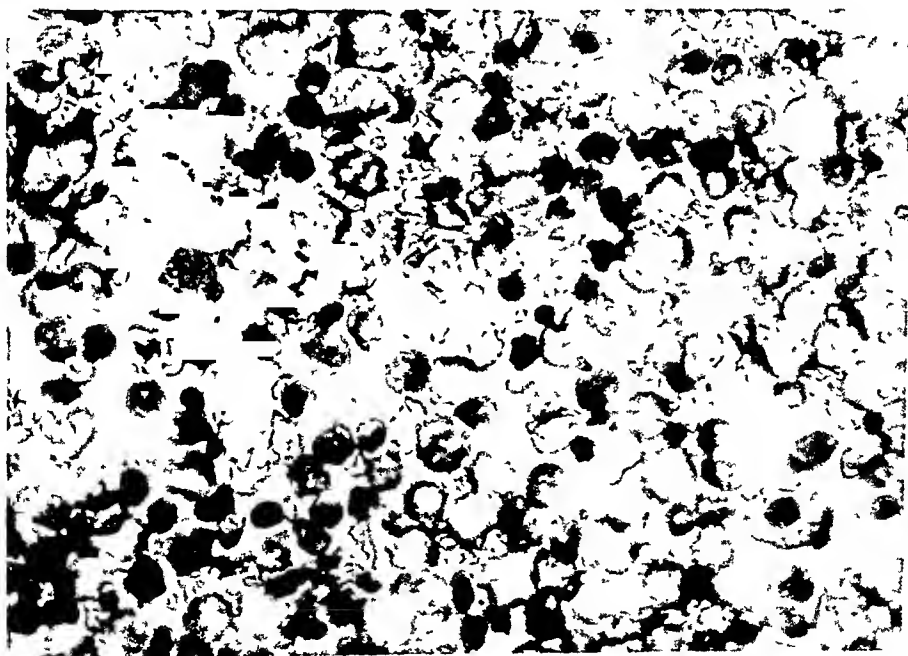


Fig. 2.—Bone marrow smear of mother showing marked cellularity as well as myeloblasts and promyelocytes (high power).

On March 6 the coagulation time as determined by the capillary glass tube method was six minutes, the clot retraction time was normal, and the bleeding time was one and one-fourth minutes. The Paul-Bunnell reaction for infectious mononucleosis was negative. The basal metabolic rate was +17, and the blood Wassermann test, as well as several blood cultures, were negative.

penicillin having been stopped two weeks previously. Under symptomatic therapy the urticaria subsided.

Analysis of the patient's blood gave the following values: icteric index, 5.2; Van den Bergh, negative; cephalin flocculation test, negative; phosphorus, 4.8 mg. per 100 e.e.; alkaline phosphatase, 3.2 mg. per 100 e.e.; total cholesterol, 191 mg. per 100 e.e.; free cholesterol, 69 mg. per 100 e.e.; cholesterol esters, 122 (66 per cent) mg. per 100 e.e.; total serum protein, 5.9 Gm. per 100 e.e.; albumin, 4.2 Gm. per 100 e.e.; globulin, 1.7 Gm. per 100 e.e.; albumin-globulin ratio, 2.47. The values for blood nonprotein nitrogen, creatinine, and sugar were normal repeatedly, while the sedimentation rate was continually elevated. Urines, electrocardiograms, and roentgenograms of the chest were unremarkable.

On April 2, when the patient was afebrile, penicillin was resumed to see if it would have any effect on the blood picture. Four days later it was discontinued when the patient left the hospital in fairly good general condition with her leucemic blood picture remaining essentially unchanged save for a lower total leucocyte count (Table VII).

*Second Admission.*—Following her discharge, the patient remained asymptomatic for three weeks until April 30, when she developed a temperature of 101° F. and had recurrent chills. When she did not respond to sulfadiazine, she returned to the hospital on May 5 complaining of diarrhea, frequency of urination, and low back pain. Examination now revealed a pale, tired patient who still did not appear seriously ill. On her chest she had a small purpuric spot. In her left axilla was a small, moderately firm lymph node, and in her right axilla, a much smaller node. The small inguinal glands noted on previous examination were still present. Again the liver and spleen were not palpable.

During this stay in the hospital the patient did not respond dramatically to penicillin given in the usual doses, her temperature returning to normal only after four weeks. On May 7, almost two months after she aborted, the patient began to menstruate again. The Rumpel-Leede phenomenon during this admission was positive, while the blood uric acid levels were normal. On May 17 the coagulation time was five and one-half minutes, the bleeding time four and three-fourth minutes. By June 2 her clinical condition had so improved that she was able to leave the hospital.

*Third Admission.*—Eleven days later, however, she returned with a slight elevation of temperature, prostration, fatigue, and severe headaches. The patient now appeared to be more seriously ill and looked very tired, exhausted, and anemic. Her temperature was 100° F. Spleen and liver were still not palpable, and the lymph nodes were unchanged. Despite massive doses of iron, liver, and vitamins, the patient's condition deteriorated steadily. She developed a transfusion reaction after the second of two blood transfusions. Penicillin therapy was then resumed for one week and discontinued at the request of the patient. Under this regime no improvement in the general condition was observed, and later she complained of profound insomnia uninfluenced even by heavy sedation.

On July 11 the patient developed a right facial weakness of the peripheral type, and a day later weakness of the left side of the face with difficulty in phonation and swallowing appeared. Since the patient was lethargic and uncooperative, a complete neurologic examination could not be done. She was found to have diplopia when viewing distant objects, but no diplopia on near vision. Corneal reflexes and voluntary facial movements were absent bilaterally. A negative Rinne test without lateralization was present. Papilledema of the right optic nerve, most marked in the nasal portion, and several large recent retinal hemorrhages were noticed. The left fundus was within normal limits. Dysarthria and swallowing difficulty were present, indicating involvement

TABLE I. SUMMARY OF PERIPHERAL BLOOD AND BONE MARROW FINDINGS OF THE PATIENT DURING THE COURSE OF HER ILLNESS

DATE	HEMOGLOBIN (%)	RED BLOOD CELLS (IN MILLIONS)	WHITE BLOOD CELLS (IN THOUSANDS)	PLATELETS (IN THOUSANDS)	EOSINOPHILES	MONOCYTES	LYMPHOCYTES	SEGMENTED NEUTROPHILES	STAB NEUTROPHILES	METAMYELOCYTES	NEUTROPHILIC MYELOCYTES	PROMYELOCYTES	MYELOBLASTS
<i>Peripheral Blood Picture</i>													
3/ 3	55	2.2	77.4	60	-	-	10	9	4	-	3	11	63
3/ 4	55	2.2	90.0	-	-	-	10	10	-	-	-	10	70
3/ 5	-	-	-	-	-	1	13	2	4	-	12	17	51
3/ 6	-	-	-	150	-	-	-	-	-	-	-	-	-
3/ 7	56	2.3	28.5	-	-	-	-	-	-	-	-	-	-
3/ 9	-	-	-	-	-	-	19	8	6	4	12	6	45
3/10	-	-	21.4	-	-	-	-	-	-	-	-	-	-
3/12	-	-	-	-	-	-	23	17	5	2	5	5	43
3/13	-	-	-	100	-	-	-	-	-	-	-	-	-
3/14	60	2.1	22.0	-	-	-	-	-	-	-	-	-	-
3/15	-	-	-	-	-	1	36	17	7	1	8	5	25
3/16	-	-	-	-	-	2	25	23	10	3	5	5	27
3/19	-	-	16.0	-	-	-	-	-	-	-	-	-	-
3/20	56	-	12.3	-	-	-	-	-	-	-	-	-	-
3/21	-	-	11.5	-	-	-	-	-	-	-	-	-	-
3/23	-	-	-	-	1	-	43	11	3	1	5	5	31
3/24	-	-	10.9	-	-	-	-	-	-	-	-	-	-
3/26	60	2.5	8.9	-	-	-	37	27	8	-	3	2	23
4/ 1	-	-	10.1	-	-	-	-	-	-	-	-	-	-
4/ 5	-	-	6.2	-	-	-	-	-	-	-	-	-	-
4/ 6	-	-	-	-	-	-	60	14	5	1	1	2	17
5/ 5	-	2.8	30.0	-	-	-	-	-	-	-	-	-	-
5/10	-	2.8	49.0	-	-	-	-	-	-	-	-	-	-
5/11	86	2.5	71.1	70	-	-	15	6	5	2	6	14	52
5/14	80	3.0	87.2	-	-	-	-	-	-	-	-	-	-
5/16	80	2.3	37.0	-	-	-	-	-	-	-	-	-	-
5/18	53	1.9	43.5	-	-	-	13	3	7	3	9	13	52
5/21	67	2.1	37.1	-	-	-	-	-	-	-	-	-	-
5/23	73	2.6	50.3	-	-	-	-	-	-	-	-	-	-
5/24	-	-	-	-	-	-	13	13	15	7	9	6	37
5/28	50	1.7	42.9	-	-	-	-	-	-	-	-	-	-
6/ 1	53	2.5	65.2	-	-	-	-	-	-	-	-	-	-
6/19	40	2.0	21.2	-	-	-	-	-	-	-	-	-	-
6/26	53	1.7	16.0	-	-	-	-	-	-	-	-	-	-
7/12	48	2.3	12.5	-	-	-	-	-	-	-	-	-	-
<i>Bone Marrow Picture</i>													
3/ 4	Marked hyperplasia; rare megakaryocytes; marked reduction of erythroid elements; normoblasts 5/100 white blood cells				1	-	3	7	3	1	10	28	47
3/16	Less cellular marrow; normoblasts 15/100 white blood cells				2	-	14	18	6	3	8	17	32
7/12	Markedly hyperplastic and myeloblastic; normoblasts 6/100 white blood cells; reduced erythroid elements				1	-	5	2	2	2	3	1	54



picture or in the fatal evolution of the disease. Our experience with penicillin confirms the reports in the literature by Herrell<sup>9</sup> and Keefer<sup>10</sup> concerning the ineffectiveness of penicillin in leucemia. It was felt, however, that the penicillin was of help possibly in controlling the superimposed intercurrent infections of the patient. Since no references concerning the effect of penicillin in acute leucemia complicated by pregnancy could be found, it is believed that this is the first such case reported.

The development of nervous system and ocular lesions during the downward course of the disease in this case was not totally unexpected. Stodtmeister and Weicker,<sup>11</sup> analyzing 300 cases of leucemia from the literature, found that the nervous system was involved much more frequently in leucemia than was generally assumed. Hemorrhages, infiltrations, and degenerative processes were responsible for the leucemic changes in the nervous system.

In one series of cases Hudson<sup>12</sup> found eye ground changes in about one-third to one-fourth of patients with leucemia. The most commonly reported fundal changes were retinal hemorrhages (as occurred in this patient) and distended veins. The cause of the papilledema in this case could not be verified post mortem, but the suspected cause was hemorrhagic involvement of the sheath of the right optic nerve with resulting impairment of the venous outflow.

The effect of pregnancy and leucemia on each other, although still not definitely determined, deserves comment inasmuch as it affects therapy and the management of such cases. Considering the effect of pregnancy on leucemia, Grier and Richter<sup>7</sup> note that there is usually an exacerbation of symptoms of leucemia during pregnancy and a remission after delivery, while Moloney and his associates,<sup>2</sup> as well as McGoldrick and Lapp,<sup>1</sup> believe that the course of leucemia is not greatly affected by pregnancy. In this case it was felt that the pregnancy had no great effect on the leucemia, which continued to progress even after the pregnancy was terminated.

Frequently an acute exacerbation of the leucemic process has been noted after parturition, the leucocyte count showing rapid increase in the number of immature cells. In this case the leucocyte count declined immediately after the premature labor, only to increase subsequently (Fig. 3).

On the other hand, the effect of leucemia on pregnancy is more clear-cut. Leucemia appears to predispose toward the spontaneous induction of premature labor. McGoldrick and Lapp<sup>1</sup> observe that, of 49 cases of acute and chronic leucemia allowed to progress in their pregnancies without interference, 21 (42.8 per cent) developed premature labor. The negative fetal blood findings and the histologic study of the fetal tissues confirm the general impression that leucemia is not found at birth in children born of leucemic mothers.

The management of pregnancy in a leucemic woman is still an unsettled problem. Forkner<sup>13</sup> comments that no rule can be made to apply to the management of cases of pregnancy complicated by leucemia, but that thorough consideration of all aspects of the problem in each case by the internist, as well as by the obstetrician, will lead to the best solution. Grier and Richter<sup>7</sup> recommend that any woman with leucemia should be advised against pregnancy.

If the pregnancy complicated by leucemia is diagnosed early, Erf and Fine<sup>14</sup> note that abortion is preferable. If, however, the pregnancy is well advanced, conflicting opinions result. Some believe the pregnancy should be interrupted because the treatment necessary to control the leucemia may injure the fetus. In his review of the harmful effects of irradiation, Rolleston pointed out that of 75 infants born of nonleucemic mothers who had been irradiated during pregnancy, 38 were not healthy, and 18 were microcephalic idiots.

Grier and Richter<sup>7</sup> feel that pregnancy should not be terminated since interference only tends to produce premature or nonviable babies and shortens the mother's life. Premature induction of labor or cesarean section is justifiable



of the ninth and tenth cranial nerves. No abnormalities of the eleventh and twelfth nerves were found. Babinski responses were equivocal, and the left Achilles jerk could not be elicited.

The patient began to menstruate profusely on July 12, but following the administration of testosterone propionate her flow decreased. She became incontinent, developed a septic temperature and went rapidly downhill. On July 22, approximately twenty weeks after the patient's initial admission to the hospital, she became comatose and expired. Permission for an autopsy was refused.

### Discussion

Despite the mounting number of cases reported in the literature, the combination of leukemia and pregnancy is still comparatively rare. In 1943 McGoldrick and Lapp<sup>1</sup> collected from the literature references to 111 cases. In only 79 was the diagnosis of leukemia associated with pregnancy well established enough for analysis. To this total they added their own case of chronic myelogenous leukemia and pregnancy. In the same year Moloney and his associates<sup>2</sup> reported a similar case, while van der Sar and Hartz<sup>3</sup> described a patient with subacute leukemia and pregnancy. During 1944, three cases of chronic myelogenous leukemia and pregnancy were recorded, two by Hochman<sup>4</sup> and one by Angelucci.<sup>5</sup> In the same year Appelbaum<sup>6</sup> reported a case of a pregnant woman with acute myeloid leukemia. Including the present account, the total reported number of unquestionable cases of leukemia associated with pregnancy is, therefore, 87.

The exact onset of the disease in this patient cannot be determined, since no blood studies were done before the beginning of the patient's illness, but it was felt that her leukemia apparently had begun during her second pregnancy. In favor of this view was the fact that she had carried on an active life with vigorous athletic activities up to the time of conception, and had considered herself healthy prior to the sudden onset of her symptoms. The myeloblastic picture of the peripheral blood and of the bone marrow, the marked prostration, and the throat lesions, together with the absence of noticeable lymphadenopathy, likewise indicate an acute leukemia process. The absence of a palpable liver and spleen and the progressively downward course of the patient with death in five months seem to confirm the diagnosis of acute myelogenous leukemia.

This case demonstrates the importance of doing complete blood counts early in pregnancy. Grier and Richter,<sup>7</sup> as well as McGoldrick and Lapp<sup>1</sup> state that acute leukemia is usually discovered during the fifth to seventh month of gestation, as occurred in this patient. Since in sepsis a marked shift to the left in the blood takes place and the blood picture may be indistinguishable from that found in leukemia, a leucemoid blood reaction due to sepsis, infectious mononucleosis, or drugs was ruled out in this case before the definite diagnosis of acute myelogenous leukemia was made.

Deserving of comment is the rather long course of the acute leukemia in this patient. In a clinico-pathologic study of 40 cases of acute leukemia, Kaufmann and Lowenstein<sup>8</sup> found the average life expectancy was 10.2 weeks, while McGoldrick and Lapp<sup>1</sup> estimated it to be 10 weeks after the discovery of leukemia. The patient described in this report lived about 20 weeks after her leukemia had been discovered. It is possible that the patient would have lived as long without penicillin, but it is felt that the administration of penicillin may have played a role in prolonging her life.

More than 3,500,000 units of penicillin were administered to the patient during the course of her illness. On penicillin therapy her leukocyte count declined steadily from 90,000 to 6,200 during her first admission (Fig. 3). Subsequently, penicillin apparently failed to create any great change in the blood

## ENDOCRINE INFLUENCES UPON THE BLOOD PRESSURE OF NORMAL AND HYPERTENSIVE RATS\*

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THE fall of blood pressure during pregnancy in hypertensive rats has been described in a previous communication.<sup>1</sup> This observation, originally made on dogs by Goldblatt, Kahn, and Hanzal,<sup>2</sup> has been amply confirmed on rats,<sup>3, 4</sup> dogs,<sup>5, 6</sup> and rabbits,<sup>7</sup> but the cause for this decline is not known. The behavior of such hypertensive animals differs from that of hypertensive women, who usually show a further rise of blood pressure in late pregnancy. The present report is concerned with the possibility that the fall of blood pressure in hypertensive rats during pregnancy is due to an altered endocrine state.

In order to study the influence of any factor upon an animal's blood pressure, spontaneous fluctuations or those due to inherent errors of observation must be well understood. Normal adult rats show a remarkably stable blood pressure from day to day, increasing only slightly with age. The mean systolic tail pressures of 21 normal female rats of the same age and weight as those utilized in the present study has been shown to be 104 mm. Hg., with a standard deviation of 5.<sup>1</sup> Relatively small variations in the mean blood pressure of a group of *normal* rats are often meaningful, as in the case of normal pregnancy illustrated below.

The clinical course of experimental hypertension in the rat, on the other hand, is frequently characterized by a labile blood pressure and occasionally by spontaneous remissions or exacerbations. The more severe the hypertension, the greater is the lability. Only one of four or five hypertensive rats was found to be suitable for the type of study reported below, for we selected only those animals demonstrating less than a 10 per cent variation from the mean blood pressure in any period of two weeks prior to the start of injections.

Foa, Foa, and Peet<sup>4</sup> stated that there was no change in the blood pressure during pregnancy in six normal rats, but apart from this there is very little known about the effects of pregnancy, lactation, or the estrus cycle upon the blood pressures of normal rats. We have made these observations as a prerequisite to the study of endocrine influences in hypertensive rats. We then attempted to duplicate certain endocrine changes which might be related to pregnancy by the injection of hormones or the induction of pseudopregnancy in groups of hypertensive rats.

### Experimental

*Methods.*—In all cases, hypertension was induced by a partial constriction of the left renal artery by means of a silk tie.<sup>8</sup> Systolic blood pressures were

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only when the pregnancy is near term. In the case under discussion, conservative therapy was used but, as usually occurs in these cases, the patient aborted spontaneously.

For the treatment of the leucemia itself, radiation and arsenic are the two best therapeutic agents at present. The use of x-ray irradiation therapy is limited to patients with the chronic forms of leucemia. But, even here, x-ray therapy should be used cautiously, since it cannot be given without danger to the fetus. The use of radioactive phosphorus, as described by Warren,<sup>16</sup> may in the future prove to be a safe means of internal radiation in this condition. However, at present, arsenic in some form is recommended to produce a temporary remission in chronic myeloid leucemia without injuring the fetus.

In acute leucemia no known form of treatment is of lasting value. Frequent blood transfusions may control the hemorrhagic tendency and prolong life for a short time. Many workers feel that treatment with arsenic or irradiation is contraindicated. From the experience with penicillin in this case, it is recommended that penicillin be tried in patients with leucemia showing signs of infection and sepsis.

### Summary and Conclusion

1. A fatal case of acute myelogenous leucemia and pregnancy treated with penicillin is reported.

2. Penicillin appeared to be of some value in combating superimposed infection, but did not materially improve the leucemic blood picture.

3. At necropsy no sign of leucemia was found in the stillborn fetus.

4. The treatment of leucemia complicated by pregnancy is still unsatisfactory.

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TABLE III-A. TWENTY-THREE NORMAL FEMALES FOLLOWED THROUGH PREGNANCY

DAY OF PREGNANCY	1-4	5-8	9-12	13-16	17-20	20+
Number of readings	27	33	24	23	26	15
Mean blood pressure	105.0	105.5	104.3	106.5	100.5	98.5
Standard deviation	6.0	5.8	6.7	5.8	6.9	5.3

TABLE III-B. SIGNIFICANCE OF BLOOD PRESSURE DECLINE IN LATE PREGNANCY

DAYS OF PREGNANCY	1-16	17-22
Number of readings	107	41
Mean blood pressure and standard error	105.2 $\pm$ 0.6	99.7 $\pm$ 0.9
Standard deviation	6.1	6.1
Difference between means = 5.5 $\pm$ standard error of 1.1		

TABLE III-C. SAME GROUP OF TWENTY-THREE RATS OBSERVED DURING LACTATION

DAY OF LACTATION	1-4	5-8	9-12	13-16	17-20	21-23	WEANED
Number of readings	17	25	24	14	18	14	24
Mean blood pressure	106	107	109	115	116	113	110
Standard deviation	7.1	6.2	5.2	5.5	6.0	8.0	5.5

that seen in the pseudopregnant state<sup>13</sup>—in all of five additional rats. No characteristic alteration of blood pressure followed, unlike the observations noted previously when deciduomas were produced.<sup>1</sup> The results are placed for convenience in columns 9 and 11 of Table IV.

*Control Injections and Criteria for Blood Pressure Changes.*—In dealing with small groups of *hypertensive* animals, a slight rise or fall of blood pressure in less than half of the group is of little significance, and will occur frequently by chance. This is illustrated in the first two columns of Table IV, in which a group of 10 hypertensive rats received 1.0 c.c. of physiologic saline daily for

TABLE IV. THE EFFECT OF HORMONES AND OF PSEUDOPREGNANCY UPON THE BLOOD PRESSURE OF HYPERTENSIVE RATS

GROUP	HORMONE	NO.	DOSAGE	HOW OFTEN	INJECTION PERIOD (DAYS)	RANGE OF MEAN BLOOD PRES-SURE	MEAN BLOOD PRES-SURE FOR GROUP	EFFECT ON BLOOD PRES-SURE (SEE TEXT)		
								DE-CREASE	NO CHANGE	IN-CREASE
1	Normal saline	10	1 c.c.	Daily	10	140-210	168	2	7	1
2	Olive oil	10	0.25 c.c.	Daily	10	142-198	170	2	6	2
3	Estrone in oil	5	0.05 mg.	Two days	16	150-216	164	1	4	0
4	Progesterone in oil	5	0.5 mg.	Two days	16	151-222	174	1	3	1
5	Progesterone + estradiol	6	3 mg. +0.005	Daily	10	149-218	171	1	5	0
6	Same plus silk threads	5	Same	Daily	10	150-163	156	0	5	0
7	Anhydro-hydroxy-progesterone	6	10 mg.	Daily	10	153-214	180	2	4	0
8	Chorionic hormone	7	500 Rat Units	Daily	10	137-213	173	1	5	1
9	Lactogenic hormone	5	1.0 mg.	Daily	14	140-158	148	0	5	0
10	Pregnant mare serum	8	10 Rat Units	Daily	10	143-190	162	0	7	1
11	Pseudopregnancy	11	Faradic stimulus to cervix during estrus (see text)			137-194	163	2	7	2

measured with a tail plethysmograph<sup>9</sup> on warmed unanesthetized rats, using a blood pressure cuff 25 mm. in length.\*

*Estrus Cycles.*—In 10 normal females, four to six months of age, blood pressures and vaginal smears were taken for thirteen consecutive days. The results are given in Table I, and show a remarkable constancy of blood pressure in all stages of the estrus cycle.

TABLE I. TEN NORMAL FEMALES FOLLOWED DAILY FOR THIRTEEN CONSECUTIVE DAYS

STAGE OF CYCLE	I	II	III	IV	V
Number of readings	18	17	12	7	73
Mean blood pressure	106	104	104	103	105

Ten moderately hypertensive females of the same age were studied similarly. Since the level of hypertension varied from 136 mm. to 170 mm. in the various animals, and since not all stages of the estrus cycle were observed in every rat, the calculations are based upon variations from the mean for each animal. The sum of these variations in any one phase of the estrus cycle was then added to or subtracted from the median blood pressure for the entire group (152 mm.). It may be seen from Table II that there is no significant influence of the ovarian cycle upon the level of hypertension.

TABLE II. TEN HYPERTENSIVE FEMALES FOLLOWED DAILY FOR THIRTEEN CONSECUTIVE DAYS

STAGE OF CYCLE	I	II	III	IV	V
Number of readings	16	12	8	7	83
Mean blood pressure (see text)	153	154	150	150	151

*Pregnancy and Lactation.*—The blood pressure was observed twice weekly on 23 normal female rats from the day of conception to the time of weaning their litters six weeks later. In every rat there was a slight decline during the last quarter (five days) of pregnancy (Table III-A). The drop of 5.5 mm. at the end of pregnancy is 5 times the standard error of the difference between the mean blood pressure for the first sixteen days of pregnancy and the mean for the last six days, and may be considered significant (Table III-B).

During lactation there was a progressive rise of similar magnitude as shown in Table III-C, and after weaning the pressure returned to a lower level. That it did not return to the exact original level may perhaps be attributed to the increased age and size of the animals at the conclusion of the experiment. Rises of blood pressure have also been observed in hypertensive rats during the lactation period.

*Pseudopregnancy.*—The induction of a pseudopregnant state in hypertensive rats is difficult because of the frequent loss of estrus cycles in such animals. By inducing estrus with small doses of pregnant mare serum, however, and then stimulating the cervix uteri with a faradic current, a pseudopregnant state was induced in 11 hypertensive rats. Lactogenic hormone (prepared and given to us by Dr. W. R. Lyons<sup>12</sup>) caused a cessation of estrus cycles—like

\*The accuracy of the measurement of blood pressure in the rat by a tail plethysmograph has been questioned recently.<sup>10</sup> We have checked the pressor responses resulting from the injection of drugs by both the indirect tail plethysmograph and by direct cannulation of the carotid artery, using a small Hertle manometer. The tail pressures are lower than the carotid pressures, but the rises produced by a given dosage of a pressor substance appear to be the same when recorded by either method. The fact that the tail pressure is lower than the absolute pressure should not affect the validity of the results. It has been claimed<sup>11</sup> that in some circumstances the warming of rats results in a rise of blood pressure. Our animals were exposed for ten minutes to a temperature of 40° C. in a thermostatically controlled ventilated box and then placed in open screen holders in an environment of 27° C. during the measurement of blood pressure.

decline of blood pressure toward the end of gestation, with a rise during lactation. These changes, though relatively slight, are qualitatively similar to the more marked fall which occurs in the hypertensive rat during pregnancy. The pseudopregnant state did not result in a decline of hypertension.

Estrone and progesterone (singly and in combination), anhydro-hydroxyprogesterone, pregnant mare serum, and chorionic and lactogenic hormones were administered in relatively large doses over a period of ten to sixteen days, and did not differ in their effects on hypertensive rats from injections of normal saline or olive oil.

The results do not justify the assumption that endocrine influences alone are responsible for the decline of blood pressure observed during late pregnancy in animals with experimental renal hypertension.

We wish to acknowledge the technical assistance of Mr. Lewis T. Brown and Mrs. Barbara Smith.

We are indebted to the following firms for their kind donations of hormones: Eli Lilly & Co. for Estrone in Oil and Progesterone in Oil; Schering Corporation for Pranone Tablets; Cutter Laboratories for Gonadin; and Ayerst, McKenna, and Harrison for A. P. L. Hormone.

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ten days. One rat showed a rise and two a fall in mean blood pressure. Subsequently this same group was injected with 0.25 c.c. of olive oil daily, and with similar results. By "decrease" or "increase" we mean that the average blood pressure during the injection period showed a change amounting to at least 10 per cent of the preinjection level.

*The Effects of Hormones.*—Selected groups of five to eight female rats weighing between 180 and 250 Gm. and having stable hypertension were given various hormones either daily (in aqueous solution) or every other day (dissolved in oil). The injection periods varied from ten to sixteen days, and blood pressure was determined every forty-eight hours. The amounts of estrone and progesterone are as large as those required for the maintenance of pregnancy after removal of the pituitary and ovaries,<sup>14</sup> and the ratio of estradiol to progesterone (column 3) is that which was found to be optimal for maintenance of deciduomas in the oophorectomized animal.<sup>15</sup>

An attempt was made to produce deciduomas by giving both estradiol and progesterone and placing silk threads in the uterus. Symmetrical enlargements of the uterus were noted a week later, but histologic examination did not reveal true placentomas and no fall of blood pressure was observed.

The anhydro-hydroxy-progesterone was administered orally by grinding the tablets with a small meal and waiting until this was consumed before further feeding. Estrone, progesterone, chorionic hormone, and pregnant mare serum were administered as indicated in Table IV. In not one of these groups was there any consistent change in the level of the blood pressure, nor any alteration in the subsequent course of the hypertension. The results are tabulated in columns 3 to 10 of Table IV.

### Discussion

As will be pointed out later,<sup>16</sup> it is the placenta and not the fetus of the rat which is responsible for the decline of hypertension in late pregnancy. Considering the results obtained in this study, it is unlikely that the endocrine changes resulting from the presence of the rat's placenta can be held responsible for the phenomenon. The hormones were administered over a period equal to or exceeding half that of pregnancy and in amounts presumably larger than those normally existent in the pregnant rat. A variety of hormones, singly and in combination, were utilized; so that a similar pronounced fall of blood pressure should have resulted in at least one of the groups if the endocrine changes of late pregnancy were solely responsible for the effect. Furthermore, if the latter were true, the estrus cycles or the pseudopregnant state should have affected the level of hypertension as well. While there are, no doubt, several possibilities, it seems likely that either the hemodynamic effect of the placental circulation or the elaboration of a hypotensive substance by the placenta accounts for the fall which actually occurs to a slight degree in normal rats, but to a marked degree in rats with experimental renal hypertension. We did not observe any rises of blood pressure from estrogens, such as those reported in normotensive rats by Grollman, Harrison, and Williams,<sup>17</sup> and Leatham and Drill.<sup>18</sup>

### Summary

In both normal and hypertensive rats the blood pressure is unaffected by the estrus cycles. In normal rats pregnancy results in a small but significant

Spalding-Richardson operation, a vaginal plastic in which the isthmic portion of the uterus alone is retained and utilized with its broad ligament and uterosacral attachments. He presents a record of 150 cases with no mortality and good results. This operation, of course, is more prolonged and more extensive than either the Manchester or vaginal hysterectomy.

In ascribing vaginal fixation to Brady, the author is rather careless in his bibliography. Many years previously, Fraenkel fully described the principles of this operation. Cystocele and incontinence of urine are very well dealt with, including well-illustrated Goeckel-Stoeckel fascial suspension and various modifications. The description of the cure for vesicovaginal fistula is very adequate, and there is also a full description of the transplantation of ureters into the sigmoid where fistulae cannot be closed, as, for example, those following radiation of carcinomas of the bladder or vagina. The author prefers the Coffey and Jewett methods of transplantation. The technique of closure of minute fistulae by fulguration is omitted. The repair of complete tears of the perineum and of rectovaginal fistulae is described, but here, as in several other places, it appears to me that too many sutures are used, or at least indicated in the illustrations, as for example Fig. 106. I can agree with the statement that 50 per cent of the hemorrhoids seen by the gynecologist are entirely asymptomatic. The treatment of anal conditions is described.

The author's judgment as to when to operate or not in the case of fibroids of the uterus is clear cut and conservative, as is his discussion as to whether to perform total or subtotal hysterectomy for this condition. He is mainly guided by the appearance of the cervix and the absence of inflammation in this area. In 300 cervical biopsies, four early carcinomas (in situ) were found. He is not too enthusiastic about performing myomectomy, certainly much less so than either Bonney or Rubin. Operative injury to the ureters is taken up. Nonmalignant ovarian lesions and their therapy are satisfactorily described. Whether the author is too sanguine that dilatation relieves some dysmenorrheas is a matter of opinion. He performs this operation regularly under pentothal sodium anesthesia.

The important condition of carcinoma of the cervix is very thoroughly treated, and the importance of early recognition of carcinoma by means of histology is emphasized. Both Martzloff's and the strictly clinical classification of the League of Nations is discussed, as well as the analysis of operative and radium statistics. In conformity with most American authors, Te Linde treats the majority of cervical cancer by means of x-ray and radium, combined. Only in very early cases is a radical panhysterectomy without gland dissection warranted. The radiation technique is entered into in considerable detail. For corpus carcinoma, radium and abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended.

Functional bleeding is treated more or less in the usual way, curettage and progesterone being the main reliances. Endometriosis is given a very detailed description, including the theory, the symptomatology, and the therapy. Operatively, much individualization is indicated. Presacral neurectomy is warranted only in patients in whom all other measures have failed. Gonorrhea and its complications are very thoroughly described, including the details of bacteriologic culture. Perhaps Te Linde might be willing to alter the statement that "those cases of gonorrhea that do not respond to sulfonamide therapy should be treated with penicillin," to first trying penicillin, since now it is so readily available. Surgical measures for residua are very detailed. I predict that this type of surgery will become rarer and rarer, as early treatment of gonorrhea will limit peritoneal infections to small numbers.

Pregnancy and its complications include the discussion of abortion in the treatment of which I am glad to see that roentgen abortion is mentioned. The operations for ectopic gestation is described in which the author mentions examination of the patient under pentothal sodium anesthesia in doubtful cases, as well as the occasional use of the peritoneoscope for both ectopic gestation and for the adequate diagnosis of small doubtful ovarian tumors, including a full description of the instruments and the techniques. For the diagnosis and treatment of sterility, insufflation of the tubes under pentothal sodium anesthesia followed immediately by dilatation and curettage does not appeal to me. There is also a very nice description of operations for implantation of tubes and ovaries as well as salpingostomy.



# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

Te Linde's *Operative Gynecology*<sup>1</sup> is a very personal book based on his own experience and the practice of Johns Hopkins Hospital. The book is a special book for those who want to practice gynecology, and especially designed for those who had a good preliminary training as hospital residents. The author justly demands a great deal for the gynecologist to be, really six requisites—he should be an expert abdominal surgeon; should know at least the fundamentals of obstetrics; should be competent to investigate female urologic conditions; should have a broad understanding of endocrinology; should be grounded in gynecologic pathology; and finally, should be competent to handle at least minor psychiatric problems. I fully agree with these minima, but wonder how many of the Diplomates of the Board of Gynecology and Obstetrics can qualify in all of these directions.

The introductory chapters dealing with preparation, anesthesia, etc., are fully adequate, and require no particular discussion. On the whole, his attitude is very conservative. I would register some protest to the use of a midline incision, except in real emergencies such as ruptured ectopic or a patient in poor condition. However, the record as to eviscerations is good; in 5,955 laparotomies, 6 eviscerations, 0.1 per cent. Incidentally, of interest is that all of these occurred in Negro women. The death rate for evisceration is high, two out of six.

The author takes the fully justified stand that much useless surgery for retroversion and retroflexion is being done. In the rare cases where operation is indicated, he uses a modified Gilliam procedure, and where, because of other complications, particularly adnexal disease, a suspension may be considered, he uses the Coffey technique. The chapter on prolapse of the uterus is detailed. A more extensive presentation of the anatomy might have proved of value. The first operation considered is the Manchester technique, of which Te Linde says that he has never used it for complete prolapse "because it scarcely seems logical that a simple anterior colporrhaphy, with suturing of the cardinal ligaments in front of the cervix coupled with cervical amputation and posterior colporrhaphy, can support the completely prolapsed uterus." From this I gather very decisively that the Manchester operation, as practiced at Johns Hopkins, in no way conforms to the Manchester operation which I and many others perform. This is borne out by his Fig. 55, which shows incomplete exposure of the lateral parametria, bringing forward what appears to be merely a fascial sling in front of the cervix and suturing, which does not involve any parametrial structures. In fact, the exposure which I and others practice would have been much better shown by his Fig. 57G', in which the base of the broad ligaments are really exposed. Therefore, what he has to say about the Manchester certainly does not apply to the extended one with which many are familiar, and statistics of which, covering more than 1,000 cases (to be published by others) show a very good record. With what the author says about vaginal hysterectomy, I am in full accord, in that 30 per cent may be expected to show poor anatomic result; also that this operation should be restricted to cases in which there is uterine disease is absolutely true. I personally have seen too many cases of prolapse of the vault in which nothing but colpocleisis promised any effective relief. Te Linde gives a very fully detailed and interesting description of the

<sup>1</sup>*Operative Gynecology*. By Richard W. Te Linde, M.D., Professor of Gynecology, Johns Hopkins University, and Chief Gynecologist, Johns Hopkins Hospital. With 392 illustrations in black and white, and 15 subjects in full color on 9 plates. 751 pages. J. B. Lippincott Company, Philadelphia. 1946.

twenty-five years he has performed myomeetomy in 35 per cent, in the rest hysterectomy. He always considers myomeetomy if the patient is under 41 years of age. He always selects it in any case where myomeetomy is the lesser operation, or if the uterus might prove useful for ventrofixation in cases where colporrhaphy is indicated. (I have avoided ventrofixation since 1932 after finding that this operation is followed so frequently by ventral hernia in prolapse, and have substituted the Manchester operation instead of ventrofixation.) The author does not consider degeneration of fibroids a contraindication to myomeetomy. The sole possibility of contraindication might be in the rare form of cirroid fibromyoma. The additional risk of myomeetomy depends entirely on the local condition and the operator's experience. Decisions should also be influenced by the wishes of the patient.

The antiseptic pre-operative preparation of the skin should be extremely careful in myomeetomy. "In nearly all cases of myomeetomy it is advised to open the uterine cavity. . . ." He prefers a midline incision in order to have ready access to either side. In my opinion, this slight advantage is far outweighed by the increase of herniation and evisceration following midline incision. He says that it is impossible to perform myomeetomy on the seal that he does without first gaining control of the arteries which supply the uterus. This was what led him to develop his special myomeetomy clamp, and, in addition, to clamp temporarily the infundibulopelvic ligaments either lateral or mesial to the ovary by means of noncrushing forceps.

The remainder of the book is really a running commentary; and very simple, clear cut, and rather artistic line drawings which illustrate every step of the numerous operations performed under varying conditions of size, position, etc., of the fibroids. In all there are 220 illustrations devoted to myomeetomy and adenomyomeetomy, the remainder of the total 241 being used to illustrate ovarian cystectomy.

The author, whenever it is humanly possible, makes his incision in the anterior wall of the uterus after making the field bloodless by his special clamp. Fibroids, as encountered, are enucleated after the capsular layer has been found. Habitually, the uterine cavity is boldly explored for submucous fibroids or polyps, which are removed, and posterior fibroids which are found accessible are enucleated through the posterior lining of the endometrial cavity. The beds of the fibroids are closed by interrupted sutures introduced by means of the Reverdin needle.

On the other hand, if the fibroids are mainly in the posterior wall, the so-called Hood operation is utilized. This consists in a transverse incision, one-half inch behind the tubo-ovarian juncture. Through this posterior flap the fibroids are removed, the uterine cavity opened for exploration, and after myomeetomy the transverse flap, which may require some thinning, is pulled over the anterior wall so that the scar is along the anterior surface of the uterus. Occasionally, when multiple small fibroids are in close juxtaposition, segments of the uterus containing these fibroids are excised (Block excision) and apparently the author does not hesitate to practically bisect the uterus down to the cervix in order to be able to remove many fibroids. The uterus is then reconstructed by comparatively few buried and deep sutures. In closing a gap in the posterior endometrium, through and through sutures, with the knots in the uterus, are used. Special attention is given to cervical fibroids which have developed alongside the vagina.

Myomectomy in pregnancy is divided into the viable and nonviable stage. In the nonviable stage the technique is like that in nonpregnancy. In the viable stage, the fetus and placenta are first delivered before application of clamps is resorted to. For adenomyomeetomy the strips of affected musculature must be taken off *seriatim* until the growth has been completely excised. Here fundal excision with re-implantation of the tubes has been practiced.

The author also describes ovarian "cystectomy," which means excision of new growths from the substance of the ovary and which he considers applicable to all nonmalignant types, including dermoids, follicle cysts, chocolate cysts, multiple adenomatous cysts, and fibromas. I cannot follow his pathology as far as "multiple adenomatous cysts" are concerned. I personally have seen too many recurrences following resection performed on pseudomucinous cysts, but fully agree with him in the case of dermoids, of which I have removed as many as 10 from the two ovaries of one patient. I likewise would hesitate to resect chocolate cysts.

In describing the operation for sterilization, not only the technique, but also the laws governing the control of this operation, the psychiatric and medical indications, are very adequately dealt with. The author mentions that 26 techniques have been published. He personally prefers the Pomcroy method, but mentions a number of others including excision of the cornual tube and the Aldridge reversible operation.

A lengthy chapter is devoted to ovarian tumors and illustrated by colored plates of the gross pathology. The chapter on retroperitoneal growths is rather inadequate. A long chapter discusses the treatment of congenital absence of the vagina, with a description of several of the operative techniques. There is a satisfactory chapter on the surgical conditions of the vulva and vagina. I suggest that the author could be more radical in the treatment of kraurosis. If this were a general method, and fully adopted, it might be quite unnecessary to consider the Basset operation for removal of the inguinal glands. Among the many other conditions taken up are abdominal herniae and diastases, emergency intestinal work, use of estrogen in the menopause, for which the author prefers the introduction of pellets.

All in all, this is a very important contribution to gynecology, because it gives a very thorough, unhurried insight into the problems, a thorough discussion of the pros and cons, a very adequate and well-illustrated guide to operations. The line drawings are particularly good. I can say without reserve that not only the budding gynecologist, but the more mature specialist will read this book with pleasure and profit.

R. T. FRANK.

*The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy*<sup>2</sup> by Victor Bonney is the leisurely, very personal account of the development of myomectomy to the nth degree by a master technician. It is a treat to read, and contains an immense amount of information which should prove of utmost value, particularly to the budding gynecologist.

Myomectomy has always been an operation considered to involve undue risks and has usually been avoided, particularly by the occasional operator. Hemorrhage and sepsis have been the main barriers. The first distinct publication on the subject known to Bonney is that of Alexander of Liverpool, who, in 1897, published his technique, which consisted of an incision through the anterior wall through which he removed as many as twenty-five fibroids. The mortality was 9 per cent, which was as good as that of hysterectomy at that time. In the intervening years, Bonney finds that the literature, both in the United States and Britain, dealing with myomectomy, is very scant. His personal interest began in 1913. In 1923, he developed his special myomectomy clamp which stops the circulation through the uterines and the cervix. In a total of 806 myomectomies, his operative mortality has been 1.1 per cent. In 40 per cent of these patients there was a single tumor. The greatest number of tumors removed in any one patient was 225 fibroids from a uterus which had reached the size of a seven months' pregnancy. There has been a recurrence of only 2.3 per cent; not a single recurrence in patients after the thirty-fifth year. In only seven patients did the menorrhagia persist; in one requiring hysterectomy; in one, curettage. Thirty-eight per cent of those who were married and wanted to have children conceived, and in that number there was only one miscarriage. In 806 cases there was only one sarcoma, the patient dying within a few months. This is such a small percentage that I wonder whether pathologic examination of all the tumors has been routinely performed. To my knowledge, at the Mount Sinai Hospital a number of cases of sarcoma have been noted after myomectomy. In almost all of these, x-ray castration was performed, and in none did recurrence or metastases develop.

The author has also performed myomectomy in cases of adenomyoma without a single recurrence and with complete relief from excessive hemorrhage and dysmenorrhea. None of these patients conceived. In looking over his private material, Bonney finds that in the last

<sup>2</sup>*The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy.* By Victor Bonney, M.S., M.D., B.Sc.Lond., F.R.C.S.Eng., Hon. F.R.A.C.S., M.R.C.P., Lond. Consulting Gynaecological and Obstetric Surgeon to the Middlesex Hospital, London; Consulting Surgeon to the Chelsea Hospital for Women; Visiting Gynaecologist to the British Postgraduate Medical School; Honorary Consultant in Obstetrics and Gynaecology to the Army, etc. First Edition. 282 pages. With 242 original drawings by the author. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York and London 1916.

The book contains many marvelous *macroscopic colored illustrations*. These cover a large number of the commoner gynecologic conditions, certainly sufficient for any student textbook. If the rarer conditions had been illustrated by means of the same technique, the book would really pass as an atlas. On the other hand, the line drawings are distinctly crude, and the microscopic pictures are mostly unclear and appear poorly focused. Except for the colored illustrations, this book offers no advantage to the English-speaking student.

R. T. FRANK.

The second edition of Mazer and Israel's *Menstrual Disorders and Sterility*<sup>4</sup> appears after an interval of five years. It is designed for students and practitioners primarily, but delves far deeper into the subject than that level of presentation. The description of pituitary and ovarian function is very detailed and clear, and will prove of interest to laboratory workers as well as to practitioners.

In the chapter on dysmenorrhea, the innumerable measures published for the relief of this symptom are reviewed. Strong repeated dilatation of the cervix is recommended. Pre-menstrual tension, *mittelschmerz*, and amenorrhea due to pituitary disorders are described. Among other causes of amenorrhea taken up is that due to primary ovarian derangement, malfunction of the thyroid gland, adrenals, and nervous system.

Uterine bleeding is another main topic. The authors first discuss systemic causes, then local organic pelvic lesions before coming to the functional bleedings of puberty and child-bearing age, as well as postmenopausal bleeding. They are to be commended for giving so thorough and detailed a description of organic pelvic lesions which may cause menorrhagia and metrorrhagia, and which must be excluded before the diagnosis of functional bleeding may be entertained.

More than 100 pages of the monograph are devoted to the subject of sterility. The influence of gross pelvic lesions, defective insemination of the cervix, and tubal factor are considered. Among the endocrine factors, amenorrhea, menometrorrhagia, anovular menstruation, even an inadequate progestin phase are discussed. In this connection I would recommend that more attention be directed to general constitutional causations, at least in evaluating the prognosis instead of focusing too narrowly upon the genital tract. Artificial insemination is discussed, including technique.

The chapters on male sterility were written by Dr. Charles W. Charny. He reports that "adequate" endocrine therapy with gonadotropins yielded good results in 10, 29, and 34 per cent of patients depending upon the nature of the semen defect. "Relative sterility" which, according to the authors, signifies "the inability to carry successfully the products of conception to term"—in my opinion is a misnomer. It is an important chapter dealing with a subject as yet not fully understood. The authors give a fair and unbiased presentation of the many facettes, conjectures, and hypotheses.

The monograph is based upon large clinical experiences, continued laboratory control, and careful study of the literature (adequate chapter bibliographies). Good judgment has been shown in not trying to subdivide and pigeon hole the many causes for symptoms into rigid classifications as so many other authors have attempted.

One might take issue with some of the therapeutic advice such as the clinical use of "water-soluble hormone of the corpus luteum," for which there is no substantiation. It might also have been well, after giving the many remedies recommended in the literature for amenorrhea, menorrhagia and metrorrhagia, dysmenorrhea, etc., to emphasize more strongly personally preferred methods which have borne the test of time. On the whole, however, this is a good book.

R. T. FRANK.

<sup>4</sup>*Diagnosis and Treatment of Menstrual Disorders and Sterility*. By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. Leon Israel, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Second Edition, Revised and Enlarged with 133 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1946.

unless they are the minute implants one sometimes encountered, as I have been obliged to re-operate too often on patients in whom this operation had been performed by others.

As far as the technique is concerned, he adds little to that I have seen commonly practiced. I must say that the suture of such a small and delicate organ as the ovary by means of a Reverdin needle seems abhorrent. For this type of reconstruction I am in the habit of using needles that the eye surgeon employs in suturing the conjunctiva.

All in all, this is a most stimulating and fascinating monograph. It shows how persistence, the experience gained on a large material, and ingenuity enable the individual surgeon to develop techniques to an undreamed-of degree of refinement and facility. However, although I pride myself on conservatism, I feel that Dr. Bouney goes somewhat too far in trying to preserve the uterus in cases of adenomyoma where, incidentally, I have run into a rare condition which I have described (intralymphatic fibromyosis) which is a slowly progressing malignancy, grossly indistinguishable from adenomyoma.

This monograph should certainly be studied by every gynecologist, and perhaps its affect on the many who, so regularly and often uncalled for, remove the uterus, may serve to reform their needless radicalism.

R. T. FRANK.

Guggisberg, editor of the *Lehrbuch der Gynäkologie*<sup>3</sup> has produced a 717 page volume. This textbook is Volume I of a series including Gynecology; Volume II, Obstetrics; Volume III, Obstetric Operations; brought out by a combination of the German-speaking universities of Zurich (Anderes), Bern (Guggisberg) and Basel (Koller).

In his introduction, Guggisberg mentions that the war has removed all German books on gynecology and obstetrics from the market, and therefore this combination of universities for women's clinics is getting out these textbooks to fill the gap, especially for medical students and practitioners. In this volume there are five collaborators, Guggisberg, Hintzsche, Ludwig, Müller, and Neuweiler, who take up various chapters.

The anatomy and the development are covered in rather a short sketchy chapter, illustrated by line drawings which are not fully adequate. Malformations of the uterus are well described in detail and illustrated in the usual way as well as by good hysterograms. In absence of the vagina, the modern skin graft methods and the nonoperative method for producing a vagina are not mentioned. Individual chapters on the constitution and the growth disturbances are included. The physiology, which is taken up by Guggisberg, is detailed, somewhat difficult to grasp because of lack of emphasis and over-recital of innumerable facts. This chapter is followed by one on functional disturbances which include not only those of menstruation, but also those of vaginal secretion and pain (dysmenorrhea). The methods of diagnosis are gone into in considerable detail. The apparatus for a Rubin insufflation test is the crude Sellheim syringe method with introduction of air. To my surprise, laminaria for the dilatation of the cervix are featured as a preliminary to diagnostic curettage. In hysterography, lipiodol is still recommended instead of the water soluble radio-opaque substances which are rapidly absorbed and produce no permanent peritonitic irritation. The chapter on myomas is very detailed, clear, and informative, as is the chapter on cervical carcinoma which appears to be the most striking of all. Associated tracts, intestinal and genitourinary, are given individual chapters. Not only sterility, but an excellent chapter on contraception is included. Hormone therapy, likewise physical, radiotherapy, vitamins, and hygiene of the female cover the concluding chapters. The hygiene of adolescence is well presented.

In review, I may say that every detail of gynecology and allied branches is taken up and presented for the student and practitioner. Operative therapy is merely indicated. Even if this is so, the treatment of prolapse of the uterus is very insufficient from an anatomic standpoint. On the whole, the amount of material included is huge. To me, a distinct fault is the drabness of presentation, the lack of any preference or individuality, and the complete omission of references, even by name, so that the student, when he has finished studying this book, has not the slightest idea of any historical connections or any individual preferences.

<sup>3</sup>*Lehrbuch der Gynäkologie*. Bearbeitet von Prof. Dr. H. Guggisberg, Prof. Dr. E. Hintzsche, Prof. Dr. F. Ludwig, P. Dr. Dr. C. Müller, and Prof. Dr. W. Neuweiler. Herausgegeben von Prof. Dr. Hans Guggisberg, Direktor der Universitäts-Frauenklinik in Bern. 717 pages. Verlag Von S. Karger in Basel (Schweiz). 1946.

mony and disproportion between fetus and mother, is discussed. The early clinical diagnosis of pregnancy is gone into, and also the fact that x-ray diagnosis is impossible until the fourth or fifth month. He then takes up biologic diagnosis, and goes into very many tests including the Frank-Berman test which he concludes is not sufficiently characteristic and clear cut, based on the investigation of one of his pupils who apparently focused more attention on the microscopic histology than upon the gross appearance of the ovaries. In turn, the various complications encountered in pregnancy, particularly fibroids and ovarian tumors, are described. The recognition of fetal death is discussed without mention of our blood test which, after the fourth month, discloses fetal death within twenty-four hours. The first portion of the large volume is concluded with presentation of prenatal care.

In part two, which is devoted to differential diagnosis, a very extended presentation of pelvic difficulties is given, including both anatomic and clinical evidence. Finally, pregnancy toxemias are discussed.

It is rather amazing that in a book which covers such a large amount of ground with so much detail, and takes cognizance of the immense amount of literature which has accumulated, no references whatever are given. The material is well digested and clarified. A large personal clinical material is included. The book is almost encyclopedic in scope, and therefore the lack of references to the literature is to be deplored.

R. T. FRANK.

### Miscellaneous.

**Early Ambulation and Related Procedures in Surgical Management** by Leithauser is a forthright and interesting monograph which places the procedure, which is gaining more and more adherence, upon a sound physiologic and well-planned basis. This by no means implies that I agree fully with the enthusiasm of the author because, to me, who heard Emil Ries and Herman Boldt in 1899 and 1907, respectively, advocating early rising, it was a personal experience connected with the beginning of my surgical career. Boldt, in 1907, would report these cases at the New York Obstetrical Society meeting where he usually aroused marked opposition.

The monograph is based on 2,047 cases, of which 1,840 were laparotomies and of which 840 patients were out of bed within three to four hours after operation. The total death rate was 14, amounting to 0.68 per cent. The object of this procedure is to control and prevent respiratory, circulatory, gastrointestinal, and wound complications, and simultaneously to stimulate rapid recovery. The patients are taken out of bed as early as two or three hours postoperatively. They go to the toilet on the second or third time they are out of bed. They are given soft diet within twenty-four to thirty-six hours if they so desire, and the ordinary appendiceal cases return to their homes on the second day. A drained cholecystectomy usually returns home within the week. What would be of real interest and importance would be to obtain statistics as to how soon these early rising patients return to their regular occupation. (I wonder whether the enthusiastic author takes into account that at the present and under present conditions, help and supervision at home may be entirely lacking. I repeatedly encounter patients today who beg to be kept in the hospital for a few additional days because they can get no assistance whatever at home.)

In discussing the physiology, the author mentions the report by Baker, et al., from the Mayo Clinic, published in 1940 and based on 172,888 surgical cases with 1 per cent thrombophlebitis and one fatality from this cause in 500 cases, which led these authors to the use of heparin and dicoumarol. Leithauser's chapters on the physiology of pulmonary, circulatory, gastrointestinal symptoms postoperatively, and the effect of early rising upon them, are excellent. The author emphasizes the importance of preventing dehydration. Preoperatively, a small nasal syphon suction apparatus is introduced and retained for twenty-four hours. A liter of water with 5 per cent glucose is given preoperatively; in the first twenty-four hours

**Early Ambulation and Related Procedures in Surgical Management.** By Daniel J. Leithauser, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit, Michigan. 232 Pages. Charles C Thomas, Springfield, Illinois. 1946.

**Conference on Diagnosis in Sterility**,<sup>5</sup> edited by Earl T. Engle, is the Proceedings sponsored by the National Committee on Maternal Health for a meeting held in January, 1945. The main object of the meeting was to discuss not only the diagnosis of sterility, but also, in the main, therapy and infertility. There are twelve articles and a concluding summary of which five deal with the male and the remainder with the female.

Laboratory examinations of semen specimens by MacLeod, clinical interpretation of semen analysis by Simmons, testicular biopsy by Charny, the role of the accessory glands of fertility by Huggins, and chronic hemospermia by McDonald are included. I can agree with Rock who, in his summary, believes that the importance of biopsy can be exaggerated. The accessory glands appear to play little role in the human being.

The diagnosing of endometrial biopsy by Hertig is a very well illustrated and conservative contribution. Interpretation of basal body temperature curves by Tompkins is of interest. The interpretation and evaluation of tubal patency tests by Normal Miller are of interest, as is the so-called "pelvic congestion" in relation to sterility by H. C. Taylor, Jr. Rock's summary, although at times flippant, is an excellent critique.

R. T. FRANK.

### Obstetrics

Haultain and Kennedy have done an excellent job in the revision of their **Practical Handbook of Midwifery and Gynaecology**.<sup>6</sup> The text is direct and concise, and the material is quite up to date with the noteworthy omission of penicillin as a therapeutic agent in puerperal and gynecologic infections. The operations to deliver are described fully; gynecologic surgery is limited, however, to a very brief presentation. The manual should be of much assistance to the returning soldier physician who wishes for a quick review of these two subjects.

PHILIP F. WILLIAMS.

**The Transactions of the Pacific Coast Society of Obstetrics and Gynecology**<sup>7</sup> has just appeared. There were no meetings or transactions in 1944 or 1945. In addition to a number of purely casuistic clinical articles, there is an interesting description of the recovery of primate eggs and embryos by Carl Hartman.

R. T. FRANK.

Leon's **Obstetric Symptomatology**<sup>8</sup> is an 800 page textbook dealing with the symptoms and differential diagnosis in obstetrics. It is meant strictly for clinical practice. The subject matter, in a very detailed and copiously illustrated fashion, describes the changes occurring in pregnancy, taking up the individual, the body fluids, hormonal changes, and then individual organ systems. It covers the fetus at term, the maternal pelvis, both normal and deformed, fetal positions, ten original cross sections of pterii at term, external and internal palpation, and x-ray of the fetus. The usual clinical examinations and pelvimetry, both external and internal, are described in a most detailed fashion. Radiopelvimetry, both har-

<sup>5</sup>Conference on Diagnosis in Sterility. Sponsored by the National Committee on Maternal Health, January 26 to 27, New York City. Edited by Earl T. Engle. 237 pages. Charles C. Thomas, Springfield, Illinois. 1946.

<sup>6</sup>A Practical Handbook of Midwifery and Gynaecology for Students and Practitioners, by W. F. T. Haultain, O.B.E., M.C., B.A., M.B., B.Ch., Obstetrician and Gynaecologist, Royal Infirmary, Edinburgh; Consulting Gynaecologist, Leith Hospital; Lecturer in Clinical Midwifery and Gynaecology, University, Edinburgh; and Clifford Kennedy, M.B., Ch.B., Assistant Obstetrician and Gynaecologist, Royal Infirmary, Edinburgh; Lecturer in Midwifery and Gynaecology, School of Medicine of Royal Colleges, Edinburgh. Third Edition, 280 pages. 47 illustrations. The Williams and Wilkins Company, Baltimore. 1946.

<sup>7</sup>Transactions of the Pacific Coast Society of Obstetrics and Gynecology. Volume XIII, Year 1945. 159 pages. Western Journal of Surgery Publishing Co. 1946.

<sup>8</sup>Semiología Obstétrica. Treinta Y Seis Clases Prácticas. Diagnósticas Y Diagnósticos Diferenciales. By Juan Leon, Profesor adjunto de Clínica Obstétrica de la Facultad de Ciencias Médicas de Buenos Aires; Docente libre de Clínica Ginecológica; Jefe de Clínica de la Clínica Obstétrica y Ginecológica "Elisio Cantón"; Médico de los Hospitales; Jefe de la Guardia Obstétrica. 797 pages. Con 501 ilustraciones (45 en colores, de las cuales 7 láminas en ctcromía) "El Ateneo," Buenos Aires. 1946.



Hughes takes up methods of administration, which are now generalized and well known, the continuous intravenous drip method, parenteral and local, either in cavities or on surfaces.

The clinical application of penicillin begins with the prophylactic use by Parritt and Mitchell; application in generalized infections (Hudson); bacterial endocarditis (Christie). It then takes up the individual uses in surgery and medicine—chest surgery, wounds, and gas gangrene, burns and plastic surgery, orthopedic surgery and fractures, osteomyelitis, hand infections, abdominal infections, sepsis of the newborn, brain and meningeal infections, venereal diseases, ophthalmology, otorhinolaryngology, dental and oral infections, penicillin in animal diseases, and a final chapter on penicillin and the general practitioner.

I have left for the last, and out of order, the chapter on Obstetrics and Gynecology by Leslie Williams, as this, after all, is of most interest to readers of this JOURNAL.

In obstetrics, prenatally it probably does not bring on premature labor or the menses, as has been frequently suspected. It naturally is used in gonorrhea of the pregnant women, the custom being to give 100,000 units in beeswax oil at night and 50,000 units in the morning so as not to obscure a developing syphilis. In syphilis of the pregnant woman, 500,000 units should be given daily in beeswax oil for seven days; also 10 injections of neoarsphenamine, at four-day intervals, and 10 injections of a bismuth salt. In 14 syphilitic women so treated, no stillbirth occurred. There is a definite indication, both prophylactically and postoperatively, in risky cesareans, keeping it up for seven days; in obstetric cases complicated by general illnesses and hemorrhages or suspected infection; also in postpartum infections, indication for it is clear. To prevent ophthalmia neonatorum 2,500 units per c.c. of solution are a safe prophylactic; for cracked nipples, 200 units per gram of vehicle.

In gynecologic conditions, it is indicated for abdominal wall suppuration, postoperatively if blood stream infection develops, in pelvic cellulitis, in adnexal inflammations and gonorrhea generally; in pyogenic infections of the vulva as a salve. The author also indicates that it might be useful as a bougie in the cervical or vaginal canal.

There is no question that the introduction of penicillin and other antibiotics have completely changed the treatment of many infections. In none of these is it more striking than in gonorrhea where it has completely superseded the abhorrent and dangerous cervical treatment formerly needed.

This book can be most highly recommended, even though, because of the newness of penicillin as a therapeutic agent, many and rapid changes may be anticipated in every branch of the subject.

R. T. FRANK.

Benda has written an authoritative monograph on Mongolism and Cretinism<sup>11</sup> which is based on a study of the clinical manifestations and the pathology of pituitary and thyroid deficiency, and mainly on 46 autopsies. According to the author, there are 60,000 living mongoloids in this country. He finds one mongoloid in 285 dispensary children. It was recognized as early as 1907, as a growth deficiency by Arthur Schüller, who called it "congenital acromieria," the opposite of acromegaly. The mongoloid pituitary is damaged during fetal life. The characteristics which make all mongoloid children appear as if they were brothers and sisters are due mainly to skull deficiency, among the other growth changes that occur. The pituitary gland of a mongoloid is small, in contradistinction to that of a cretin, whose pituitary is large. Examination of 46 mongoloid pituitaries showed only three normal. Fifty-four per cent showed castration cells. If the thyroid is found to be colloid, there is a predominance of eosinophiles in the pituitary.

The various endocrine glands are discussed in detail, both for mongoloid and the cretin. The author believes that to avoid mongolism, the pregnant mother should be treated. Direct

<sup>11</sup>*Mongolism and Cretinism. A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency.* By Clemens E. Benda, M.D., Director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass., Instructor in Neuro-pathology, Harvard Medical School, Assistant in Psychiatry, Massachusetts General Hospital, Lecturer, Postgraduate Seminar, Massachusetts Department of Mental Health 310 pages. 101 illustrations. Grune & Stratton, New York. 1946.



postoperatively, 4 liters of water is given with 9 Gm. of sodium chloride, partly by subcutaneous route. No enema or cathartics are given on the day of operation. As contra-indication to early rising, only profound shock, hopeless conditions as carcinoma, midline rectus incision, or an insecure suture technique would be considered. No morphine is given after the first twenty-four hours. The first bowel evacuation can wait for several days or up to a week after operation. Catheterization is rarely necessary in patients who get up early. In cystocele operation, a retention catheter is kept in situ for twenty-four hours, and yet these patients are treated as early ambulators.

Several interesting chapters deal with the operative techniques of the author, particularly the placing of his incisions. Transverse or gridiron incisions are advocated. The peritoneum and transversalis is sutured with 000 chromic catgut and for fascia, 32 alloy steel is used. A subcuticular metal suture is used for the skin. Drainage of either appendix, gall bladder, or any other intra-abdominal incision, if indicated, does not prevent early rising. An analysis of the operations performed and a detailed analysis of all of the fatal cases are given.

Thorough study of this monograph by all surgeons who are not yet converted to early ambulation is suggested.

R. T. FRANK.

*Penicillin, Its Practical Application*,<sup>10</sup> which appeared under the general editorship of Professor Alexander Fleming, is really a *must* for anyone who intends to produce, market, or use penicillin widely. It is an all-British product, having twenty-eight contributors whose independent views do not show too much conflict. The book is intended for the practitioner, and shows him how to use penicillin to the best advantage. It likewise includes two chapters on dental and veterinary practice.

The senior author, Fleming, writes an introduction and a chapter on "Bacteriological Control of Penicillin Therapy." Few will agree with his remark, "My own contribution to this book is small. . . ." He recommends that it is "better to give more than enough than too little" because to all intents and purposes penicillin is a nontoxic substance. He describes how he discovered it in 1928 as a contaminant in a culture plate of staphylococci; how the flora grows in chains; how penicillin was concentrated 1,000 times in 1940; how the International Unit which equals 0.0006 mg. of pure crystalline sodium salt of penicillin II (United States, penicillin G) was evolved. This corresponds to 5,000 units, equalling 3 milligrams in weight.

It is quite impossible to discuss the really enormous amount of facts contained in this text and source book in the form of a review. A few chapters will be mentioned. Chemistry (Bacharach and Hems) shows that the substance, if the  $\beta$ -lactam formula is accepted, is a monocarboxylic acid, to be used as a sodium or calcium salt. The production and manufacture have now become a huge industry. Surface growth has been abandoned in favor of deep growth in 2,000 to 10,000 gallon tanks. The main steps are aeration, agitations, and asepsis. The production has been greatly accelerated by the use of "corn steep liquor."

Under pharmacy (Berry), the lack of toxicity, the sterility, the use of either calcium or sodium salt, the storing at less than 50 degrees Centigrade, the drying and freezing at pH 6.5, the incompatibilities (mainly aqueous sulfonamide solutions strong alcohols), and the various preparations such as aqueous, oily, cream, unguents, and troches are described.

The pharmacology by Garrod is important. Among other things, it shows that 60 per cent of penicillin is excreted in the urine; that unless the blood level is raised and unduly high, no entrance into the cerebrospinal fluid is observed, and that oral dosages must be about five times that of parenteral.

The chapter on bacteriological control of penicillin therapy by Fleming shows the rapid method of assay which is now essential during the course of mass production; also the estimation in body fluids, urine, etc.

<sup>10</sup>*Penicillin, Its Practical Application*. Under the General Editorship of Professor Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London, St. Mary's Hospital, London. 380 pages. The Blakiston Company, Philadelphia. 1946.

The present fourth edition of Meredith's *Hygiene*<sup>15</sup> has been rewritten to incorporate the public health advances of the war period. The book is intended for the college student, but it is equally appropriate to the interested general public at large, since emphasis is made on the fact that individual health means good community health.

The material is logically arranged, and after taking up the general health problems of the human body and the body politic, the author discusses infections, the degenerative diseases, some surgical situations, accidents, with an excellent presentation of habit-forming drugs.

The seventh part of the book details the aspects of everyday personal hygiene, in which the important part of nutrition is stressed. The gynecologist will approve of the considerable space and scientific exposition of the reproductive processes, as well as the section on cancer.

Such a book merits a place in the family library, as well as in the college curriculum.

PHILIP F. WILLIAMS.

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<sup>15</sup>*Hygiene*, a textbook for college students on physical and mental health from personal and public aspects, by Florence L. Meredith, B.Sc., M.D., Professor of Hygiene and Public Health, Tufts College. Fourth Edition. 805 pages, 155 illustrations. The Blakiston Company, Philadelphia and Toronto. 1946.

treatment of mongolism is impossible until we obtain an active pituitary gland substance which as yet has not been possible. He believed that if the pituitary of immature animals could be obtained, such an extract might perhaps be developed.

R. T. FRANK.

The author of this book, *Sex, Marriage and Family*,<sup>12</sup> has been vitally interested in the problems of the marriage relationship, and is thoroughly qualified to discuss these topics. Dr. Rice has gathered together in one volume the essence of his many contributions to benefit the lay public on these questions. Such phases of marriage as birth control, reproduction, and the necessary adjustments in marriage for incompatibility, frigidity, impotence, and sterility are discussed. The changes in relationships as married life proceeds, the raising of a family, changes in economic situations, the menopause, and infidelity are dealt with fully and clearly. An outstanding section of the book is the consideration of the choice of a mate, while the problems of sex and marriage in relation to the war are fully discussed.

The book has been written in such a spirit of dignity and frankness as to make it an outstanding volume on the subject. It can be highly recommended for the instruction for those of the lay public who may have marriage problems to face.

PHILIP F. WILLIAMS.

This small volume, *Sex Problems of the Returned Veteran*,<sup>13</sup> by Dr. Kitching, deals frankly and wisely with the problems created for many married people by the recent war. It may be read with profit by the husband and wife, their parents, advisers, and medical counselors, for it explains clearly the effect of the artificial and unnatural separation by war upon both partners. Dr. Kitching discusses separation anxiety and its physical, emotional, and spiritual results. The wife's problems are no less sympathetically reviewed than those of the soldier who has served on foreign soil. The psychological impact of the reunion anxiety are analyzed and the problems of remarriage and readjustment and their solutions are skillfully handled.

Such an informative book should be of inestimable value to those in the profession to whom the returned soldier and his wife may turn for help on their sex problems.

PHILIP F. WILLIAMS.

This detailed compendium on *Regional Anesthesia*<sup>14</sup> presents the work of Dr. Pitkin, with contributions by present-day workers on all types of regional, refrigeration, spinal, and epidural anesthesia. The editors and contributors are well qualified in their respective lines, and have clearly, completely, and concisely covered the field from the standpoint of anatomy, rationale, and technique. The description of the text has been enriched by the great number of illustrations. The modern concept of, and necessity for, regional blocks in surgery and therapy are convincingly handled. The index is complete and well organized. Of particular interest to obstetricians and gynecologists is the section on continuous caudal block, its indications, contraindications, and accomplishments. While the text appears to be primarily of value to the specialist in anesthesia, it is an excellent reference work for the general or specialist surgeon.

PHILIP F. WILLIAMS.

<sup>12</sup>*Sex, Marriage and Family*, by Thurman B. Rice, A.M., M.D., Professor of Bacteriology and Public Health, Indiana University School of Medicine; Author of "Sex Education Series," American Medical Association; Chairman of Joint Committee on Health Education of National Educational Association and the American Medical Association, J. B. Lippincott Company, Philadelphia and New York, 1946.

<sup>13</sup>*Sex Problems of the Returned Veteran*, Howard Kitching, M.D., Foreword by Ernest B. Groves, Professor of Sociology, University of North Carolina, 124 pages, Emerson Books, Inc., New York, 1946.

<sup>14</sup>*Conduction Anesthesia, Clinical Studies of* George P. Pitkin, M.D., F.A.C.S., F.I.C.A., edited by James L. Southworth, M.D., and Robert A. Hingson, M.D., with chapters prepared by the following collaborators: Winifred Pitkin, M.D., M.R.C.S.; A. R. McIntire, M.D., Ph.D.; Frederick M. Allen, M.D., F.A.C.P.; Waldo B. Edwards, M.D.; Louis A. Palmer, M.D., F.A.C.S.; William T. Lemmon, M.D., F.A.C.S.; Lyman W. Crossman, M.D., F.A.C.S.; Henry G. Hager, Jr., M.D., 336 pages, with 696 illustrations, J. B. Lippincott Company, Philadelphia, London, Montreal, 1946.

## Abortion

Stefancsik, S.: *Etiology of Abortions*, *Monatsschr. F. Geburtsh. u. Gynäk.* 119: 23-33, 1945.

The author maintains that when abortion occurs in the presence of genital hypoplasia, the cause is imperfect development of the cervix. That the cervix is an important cause of abortions may be seen from the cases of abortion which follow amputation of the cervix, injuries and tumors of the cervix, and from comparative obstetrics in animals. As a prophylactic measure, in cases of defective development of the cervix, the author recommends treatment before pregnancy by means of hormones as well as vitamins, regulation of the mode of living, etc.

J. P. GREENHILL.

## Anesthesia, Analgesia

Onofre de Araujo, J., and Nobrega, M.: *Present Status of Obstetric Anesthesia*, *An. brasil. de ginec.* 19: 345, 1945.

The advantages of close collaboration between obstetricians and anesthetists in the choice of anesthetic are stressed. Obstetric anesthesia differs considerably from surgical anesthesia because, besides suppressing pain, the presence of the fetus in intimate connection with the maternal system and the special conditions of the muscular birth canal, which must be preserved during labor and after delivery, requires special consideration. After a review of different methods of analgesia, of their advantages and disadvantages, the authors recommend the use of antispasmodic drugs during the first stage followed by cyclopropane-oxygen administration during the expulsion period on account of its high percentage of oxygen. For operative deliveries, the authors favor general anesthesia only for operations of short duration, such as version and extraction. For cesarean section spinal anesthesia is considered by the authors to be the method of choice when used by skilled anesthetists. Peridural anesthesia is not advocated by the authors.

The advantages of local anesthesia for normal labors, and particularly for forceps deliveries, are stressed. According to Brazilian bibliography fewer accidents of the lower birth canal are liable to occur with this type of anesthesia than any other, due to greater perineal distensibility permitted by local anesthesia.

J. P. GREENHILL.

Editorial—*Anesthesia for the Pain of Uncomplicated Childbirth*, *Anesthesiology* 6: 410, 1945.

The medical profession and their allies are still striving for the "perfect" analgesia and anesthesia for the relief of the travail of childbirth. This effort was begun some ninety-eight years ago and bids fair to continue for another ninety-eight years before a completely satisfactory solution of the problem shall have been accomplished. During all these years every new anesthesia or technique introduced into the practice of surgery or used for the relief of pain has been tried in obstetrics, beginning with chloroform in 1847 and culminating with continuous caudal in 1945. Varying degrees of success has crowned these efforts. Despite the overflowing enthusiasm of certain obstetricians and the tumultuous acclaim of the lay press, the perfect obstetric analgesia and anesthesia has not been discovered. In fact, such enthusiasm plus the "half-baked" journalistic propaganda on painless childbirth has created a problem within its own sphere. In retrospect, we might divide the sum total of all efforts into "eras" and call them the "chloroform era"; the "twilight sleep era"; the "barbiturate amnesia era"; and finally the "caudal anesthesia era." Spinal anesthesia has been "sandwiched in" in practically all of these eras but, due to the hazards involved, it has never become a universal method. The advantages and disadvantages of continuous caudal anesthesia are still being debated by the conservatives.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Pregnancy, Physiology

Baird, Dugald: The Influence of Social and Economic Factors on Stillbirths and Neonatal Deaths, *J. Obst. & Gynaec. Brit. Emp.* 52: 359, 1945.

In a previous paper prematurity was shown to be an important cause of stillbirth and neonatal mortality in Social Classes III, IV, and V of the community. In Scotland the incidence of prematurity is greater than in England, and the excess of neonatal mortality in Scotland is due largely to prematurity. Prematurity has an incidence almost twice as high in Social Classes III, IV, and V as in Classes I and II. In the former classes 50 per cent of the prematurity is "unexplained" in relation to any definite obstetric condition; the most common obstetric condition associated with prematurity is eclamptic toxemia and this is twice as common among the poor as among the well-to-do. Further studies have shown that the incidents of stillbirths has fallen steadily in Scotland, as well as in England and Wales since 1939. The fall has been greatest in those cases of unknown cause and those due to trauma and toxemia. The neonatal deaths in the first three days of life (which are due chiefly to the same factors as stillbirths) have also shown a lower incidence since 1939, while the incidence of infant deaths at 4 to 28 days of age, due chiefly to infection, has shown comparatively slight reduction. Since the incidence of prematurity cause unknown, toxemia and congenital debility of the newborn has been much higher in Social Classes III, IV, and V than in Classes I to II, the evidence indicates that the reduction in stillbirths and neonatal mortality is due to the improvement of the social condition of the poorer classes, and especially to improved nutrition, better employment, higher wages, and better distribution of milk and other essential foods under wartime regulations. This wartime experience suggests that with further improvement in nutrition and in obstetric care, a further decrease in stillbirth and neonatal mortality rates will occur. How far the high stillbirth and neonatal mortality rates in the poorer classes have been due to faulty diet during pregnancy and how far to undernourishment in youth with resulting poor physique, it is difficult to determine. In the former case, the condition can be corrected quickly, in the latter only by a long-term policy.

HARVEY B. MATTHEWS.

Hudson, Gwen S., and Rucker, M. Pierce: Spontaneous Abortion, *J. A. M. A.* 129: 542, 1945.

The authors report on their statistics in 1,000 consecutive pregnancies. Ninety-four spontaneous and 68 threatened abortions occurred in this group. Treatment with bed rest and progesterone was followed by recovery in 43 per cent of the cases. Three of the patients that were treated successfully had deformed babies. Falls and intercurrent infections were of no etiologic consequence in this series. Pelvic inflammatory disease was encountered three times, but two of these patients aborted. Overweight patients, those with low basal metabolic rates, and those who have a history of sterility were prone to abort; 44.1 per cent of the patients who aborted had retrodisplacement of the uterus on postpartum examination, as compared with 26.9 per cent of those who had full-term deliveries.

WILLIAM BERMAN.

31 per cent; Grade Three, 50 per cent; Grade Four, 12 per cent. The difficulty of accurately grading these patients is emphasized. As to the correct classification of grading, one will more often be correct if he classifies the patient as the more advanced type.

The treatment plan for carcinoma of the cervix at the Charity Hospital utilizes the technique of several investigators. X-ray therapy is an essential part of the radiation treatment and is not an auxiliary measure.

This report is based on 716 unselected cases of cervical carcinoma. The absolute three-year survival rate for the group is 37 per cent and the five-year survival period is 28 per cent. The authors are convinced that the highest salvage in all "Grades" of carcinoma is obtained from radiation therapy, no surgery being indicated in the majority of cases.

WILLIAM BICKERS.

Glatthaar, E.: Leucoplakia and Squamous Epithelial Carcinoma of the Portio, *Monatschr. f. Geburtsh. u. Gynäk.* 120: 33-45, 1945.

The author emphasizes that the clinical picture of leucoplakia may be produced by a number of different histologic changes. He differentiates between benign and malignant leucoplakias. The latter is a superficial type of carcinoma. Heretofore, no one has succeeded in proving a malignant transformation of a cervical leucoplakia by histologic study. Such a change was demonstrated by the author in a 37-year-old woman both by colposcopic and histologic examinations performed at frequent intervals during a period of eighteen months. This case is important in presenting data on the development of squamous-cell carcinoma of the cervix and so-called atypical benign epithelium of the cervix. The author maintains that colposcopic and histologic studies must be made in cases where changes appear in the cervix.

J. P. GREENHILL.

Donaldson, Malcolm: Some New Facts Concerning the Prognosis and Treatment of Carcinoma of Cervix by Radiation, *Proc. Roy. Soc. Med.* 39: 10, 1945.

The author divides his tumors into two types: the differentiated which he calls anaplastic squamous, in which the cells when young resemble normal basal cells, but when growing old they either undergo normal keratinization giving rise to typical cell nests or they undergo abnormal keratinization giving rise to an aggregation of basal cells round a necrotic core. In undifferentiated tumors called anaplastic parakeratotic, the cells when young are capable of active mitosis but degenerate as they get older by a process of cytoplasmic condensation or by nuclear disintegration. The differentiated tumors predominate in the early stages and the undifferentiated tumors in the late stages.

The author has attempted to work out the prognostic index of certain tumors by a quantitative study of postradiation sections for comparison with the pre-radiation section. Counts are made of resting cells, mitotic cells, differentiating cells, and degenerating cells. All counts are plotted on a graph. Biopsies are then taken on at least two occasions after the treatment has begun. The histologic evaluation is made within three weeks of beginning of treatment. A chart is given showing the number of agreements and disagreements between the clinical and histologic evaluation of treatment.

WILLIAM BERMAN.

### Cesarean Section

Ricci, James V., and Marr, James P.: The Physick-Sellheim Principle of Extraperitoneal Cesarean Section, *Am. J. Surg.* 71: 3, 1946.

The authors present a series of 175 cases of extraperitoneal cesarean sections with a brief analysis of the mortality, morbidity and complications encountered. A technique is described which divides the extraperitoneal operation into two major steps—(a) the liber-

That the method has distinct advantages cannot be doubted; that its disadvantages are many and often extremely hazardous to the mother cannot be denied. Furthermore, the technique of its administration is exacting and special attention is required by the patient. All of these obstacles add up to a problem that cannot be satisfactorily solved under present-day conditions in our hospitals. The lay press further complicates the picture by claiming "heavenly oblivion to the travail of parturition," thus encouraging the patient to demand something that she cannot get. Result—disillusionment and anguish on the part of the patient; disgust and vexation for the doctor. In conclusion, the author states: "From the standpoint of ideal conditions, the medical profession and its pain-controlling specialists, the anesthetists, cannot be highly satisfied or pleased with a review of their achievements in controlling the pangs of parturition, and eagerly welcome any suggestion of a satisfactory approach to the perpetual problems of painless childbirth."

HARVEY B. MATTHEWS.

Rabago, José: Anesthesia in Cesarean Section, *Gac. méd. de México* 74: 591-600, 1944.

According to the author, spinal anesthesia given according to the described technique and respecting strictly its contraindications, is the anesthesia of choice.

The contraindications are cardiac insufficiency, even if it is slight, maximal arterial pressure below 105 mm. due to any cause whatever, and hemorrhage during pregnancy or labor.

The following details of technique must be observed. (1) Lowest possible puncture, i.e., between the fourth and fifth or between the third and fourth lumbar vertebrae. (2) Puncture and injection with the patient sitting up and then changed to dorsal decubitus until frank signs of anesthesia appear in the lower extremities. (3) Injection of 12 to 15 centigrams (depending on the weight of the patient) of novocain, seurocain, or procain dissolved in 2 c.c. of cerebrospinal fluid. (4) Avoidance of escape of cerebrospinal fluid during preparation of the solution. (5) Subcutaneous injection of an ampule of cardiazol-ephedrine immediately after injection of the solution. (6) Trendelenburg position until the moment of opening the peritoneum. (7) Constant observation of pulse and arterial pressure to administer in time the necessary cardiac stimulants during the operation.

The author has had only one death that could be charged to spinal anesthesia: the injection of cardiazol-ephedrine was overlooked and death occurred twenty minutes after the anesthetic was given.

Inhalation anesthesia should be used in cases in which spinal anesthesia is contraindicated and the general condition of the patient allows it. Intravenous anesthesia with barbiturates endangers the life of the fetus. Epidural anesthesia is now being studied, but is not devoid of risks. Local anesthesia is innocuous and must be used in cases of grave visceral insufficiency, intense anemia, hypotension, etc. Its generalized use is desirable.

J. P. GREENHILL.

### Cancer, Malignancies

Graffagnino, Peter, and McPetridge, Elizabeth: Carcinoma of the Cervix. An Attempted Follow-up Study of 500 Cases, *New Orleans M. & S. J.* 98: 307, 1946.

A follow-up study on 500 women with carcinoma of the cervix covering a period of five and one-half years is reported. Of this group 183 were white; 317 Negro. Known to have died during the five and one-half year period are 358 patients from the total number, and 39 are known to be alive for periods varying from seven to twelve years after treatment. Of 29 patients with carcinoma of the cervical stump there are four survivors.

The histologic types were as follows: epidermoid, 4 per cent; adenocarcinoma, 7 per cent; squamous, 23 per cent; transitional, 31 per cent; and carcinoma (type not specified), 31 per cent. The entire group studied from the standpoint of "Grade" according to the League of Nations' classification was as follows: Grade One, 7 per cent; Grade Two,

On the other hand, it was possible to raise the temperature by an administration of progesterone. These observations suggest that the effect of progesterone extends beyond the endometrium to the thermal regulatory mechanism.

J. P. GREENHILL.

### Endometriosis

Medina, J.: Internal Endometriosis. Its Relationship With Carcinoma of the Body of the Uterus, *An. brasil de ginec.* 10: 189-197, 1945.

Carcinoma in the presence of internal endometriosis is rare. The author reports three cases which proved the transition from endometriosis to corporeal carcinoma. He accepts Robert Meyer's criterion that "the glands showing carcinomatous changes should be surrounded by cytogenous tissue." Seven illustrations prove the author's contentions.

J. P. GREENHILL.

Arenas, N., and Blanchard, O.: Perforating Endometriosis of the Posterior Fornix, *An. brasil de ginec.* 10: 129-135, 1945.

The author reports a case of perforation of endometriosis of the posterior fornix with involvement of the rectovaginal septum and inflammatory lesions of the adnexa. An operation was performed during which both tubes and ovaries were removed.

J. P. GREENHILL.

Balfour, D. C., Jr.: Endometrioma of the Urinary Bladder. Report of Five Cases, *Proc. Staff Meet. Mayo Clin.* 20: 129, 1945.

The author reports five cases of endometrioma of the bladder treated at the Mayo Clinic. All patients had urinary symptoms. All five patients had undergone previous pelvic operations. The author warns against substitutional hormonal therapy after artificial menopause for relief of this condition.

WM. BERMAN.

### Gynecology

Kovacs, F.: The Significance, Diagnosis, and Treatment of Female Genital Tuberculosis (Experience in 191 Personal Cases), *Monatschr. f. Geburtsch. u. Gynäk.* 116: 24, 183, 1943.

A personal series of 191 private cases of genital tuberculosis in women proves that this disease occurs more frequently than is generally supposed. Curettement and histologic examination of the curetted material are the most important methods of making a diagnosis. Since sterility is the rule in cases of genital tuberculosis, the endometrium should be studied in all cases of sterility and menstrual disturbances. There is no danger of spreading the tuberculosis if the curettement is properly performed.

Conservative therapy is ineffective in the treatment of genital tuberculosis. The proper therapy is surgical removal of the uterus and tubes. Since the patients are sterile anyway, no harm is done. The ovaries may be retained. The presence of tuberculosis elsewhere in the body, such as in the lungs, is no contraindication to operation, provided the operation will not seem to be too difficult.

J. P. GREENHILL.

### Gynecologic Operations

Guenin, R.: The Madlener Technic of Sterilization, *Monatschr. f. Geburtsch. u. Gynäk.* 116: 172-173, 1943.

At the Geneva Woman's Clinic, 135 Madlener sterilizations were performed, with the Walthard modification. The indications were as follows: eugenic and social indications, 24.8 per cent; obstetric and gynecologic, 25.2 per cent; and strict medical reasons, 50 per cent.



ation of the anterior peritoneal fold from the upper bladder surface and dome: (b) the liberation of the posterior peritoneal fold from the posterior surface of the bladder and lower uterine segment. The steps are shown by 19 well-illustrated drawings.

JAMES P. MARR.

**Sala, S. L.: Prophylactic Intraperitoneal Sulfonamide Therapy in Cesarean Section, *Semana méd.* 1: 354-358, 1945.**

The author presents 21 cases with ovular infection operated upon by cesarean section followed by intraperitoneal instillation of sulfonamides, without mortality. He has collected from the literature 185 contaminated cases treated with the sulfonamides with a 0.5 per cent mortality due to peritonitis; this figure is evidently lower and minimal when compared with the same kind of cases treated by other procedures. If this success continues, greater optimism for late cesarean section will lead more frequently to a test of labor and thus to more vaginal deliveries. To confirm definitely the optimistic figures offered by the method, he requests other authors to publish their clinical cases.

J. P. GREENHILL.

**Infante, Thomas R.: Hemostatic Cesarean Section in a Case of Severe Placenta Previa, *Rev. médica cubana* 56: 179-183, 1945.**

The author reports that the patient under consideration who was in shock was given 500 c.c. of gum acacia serum, and then a blood transfusion. A vaginal examination was made just before the operation. The author emphasizes that it is imperative to have another transfusion ready if such an examination is to be made. The low cervical cesarean section is strongly recommended by the author because Greenhill and Bloom pointed out that the resulting scar following cervical cesarean section is sufficiently strong to withstand the strain of subsequent labors. This type of cesarean section requires rapid, expert action by the surgeon. The use of the sulfanilamides is suggested for preventing infection.

J. P. GREENHILL.

## Endocrinology

**Held, E.: The Follicle Stimulating Action of the Urine of Puerperal Women Is Due to a Hypophyseal Substance, *Monatschr. f. Geburtsch. u. Gynäk.* 119: 214, 1945.**

The author investigated the fundamental difference which exists between the follicle-stimulating action of castrate urine and that of urine from pregnant women. Injections of the former into guinea pigs lead to the growth of many follicles while injections of urine from pregnant women resulted in the development of only a few follicles. Earlier research had revealed that the action of the pregnant cervix is due to a substance from the anencephalus-pituitary system, generally designated as pituitary. Based on this evidence the urine of puerperal women was studied for its gonad-stimulating effect. It was found that the follicle-stimulating of this urine is the same as that of the urine of pregnant women. Hence, we are dealing with a gonadotrophic hormone of chorionic origin and not one from the pituitary.

J. P. GREENHILL.

**Thermogenic Effect of Progesterone, *Lancet* 2: 663, 1945.**

Variations in waking temperature are so closely linked with the phases of the ovarian cycle that they probably depend upon ovarian secretion. The administration of extracts of whole ovary and of follicular fluid to a series of oophorectomized animals and menopausal women resulted in no effect on the waking temperature. Similarly, there was no effect upon the waking temperature upon the administration of natural estrogens.

Among the author's ten personal cases, two were delivered spontaneously, one of which was premature and macerated and was delivered by the Roederer mechanism. The second spontaneously expelled fetus was a 6 to 7 months' abortion which was delivered by the Douglas mechanism. Two babies were delivered by version and extraction. In five cases the fetus was dead, hence decapitation was performed. In one case, rupture of the uterus occurred. Peritonitis followed laparotomy and death resulted.

J. P. GREENHILL.

de Gouvea, L. R. L.: A Case of High Forceps With Inverted Atypical Grasp, *An. brasil de ginec.* 17: 1944.

The author used a modification of Llamas Massini's inverted grasp with forceps in a case of transverse arrest where he could not rotate the occiput anteriorly either manually or even with the application of Simpson forceps on the fronto-mastoid diameter. The posterior blade of the forceps was first inserted, then the anterior. The head was flexed, the posterior asynclitism was corrected, the head pulled downward and then rotated to an occiput sacral. The forceps were reapplied and the baby delivered without any perineal laceration or injury to the child.

J. P. GREENHILL.

Johansson, H.: Spontaneous Delivery of a Live Full-Term Baby in the Mentoposterior Position, *Monatschr. f. Geburtsch. u. Gynäk.* 120: 122-128, 1945.

The author reports a case of spontaneous birth of a full-term living baby in the mentoposterior position. The head was delivered with the frontal suture in the left oblique diameter of the pelvic outlet. The anterior parital prominence therefore was pressed against the lower border of the symphysis and filled the space under the pubic arch. Spontaneous delivery was accomplished by lateral dorsal flexion of the head. There are four similar cases reported in the literature, and in all of these cases the live, mature baby was delivered through an oblique diameter of the pelvis.

J. P. GREENHILL.

Perez G. Lozana, J. L.: One Hundred Cases of Oblique Presentation, *Rev. Españ. de obst. y ginec.* 2: 166-177, 1945.

Among 100 cases of oblique presentations observed at the University of Santiago the causes were as follows: contracted pelvis, 28; pendulous abdomen, 18; multiple pregnancy, 8; fetal gigantism, 4; prematurity, 4; placenta previa, 2; hydrocephalus, 1; arcuate uterus and elderly primipara, 1 each; and undetermined origin, 33. The parity varied from one (18 cases) to 12. Seventeen women were admitted to the hospital with intact membranes, 25 had ruptured membranes with a living fetus, 54 had ruptured membranes and a dead baby, and four women were admitted with rupture of the uterus. Twelve of the 17 women with intact membranes were treated by external version and five by cesarean section. In the second group treatment was chiefly by version under deep anesthesia followed by manual extraction. In the third group 47 were delivered after decapitation, and five by version and extraction. The fetal mortality was 63 per cent and the maternal death rate was 6 per cent.

The only complication in this series was a case of ileus observed ten months after the operation. The patient died from peritonitis. No other disturbances were observed following the operations.

J. P. GREENHILL.

**Bertrand, I., Mazars, G., and Godet-Guitlain, J.:** Electro-Encephalographic Changes Associated With Uterine Curettage, *Presse méd.* 53: 352, 1945.

It has long been known that nervous accidents may be associated with intrauterine manipulations. Most of these accidents occur after intrauterine attempts to produce an abortion. The accidents usually consist of convulsions, generalized or followed by hemiplegia. Death also may follow brisk cervical manipulation. In most cases, accidents which follow cervical trauma and intrauterine operations are blamed on air embolism, but the authors believe this is erroneous. The analogy between accidents after uterine manipulation and pleural puncture leads the authors to study the electro-encephalograms of patients who had intrauterine operations, and they found that there is a uterine reflex just as there is a pleural reflex.

The authors curetted thirteen women without anesthesia and with as little pain as possible. Before the operations the encephalograms were normal, but during manipulation of the cervix the picture changed, and during the actual scraping marked changes were observed. In only two of the thirteen women were the tests negative. Swabbing the uterine cavity produced the same changes as curettement. After the operation the encephalograms rapidly returned to normal. Hence these studies show that intrauterine manipulations, especially at the tubal corners, produce an undeniable cerebral effect, most often unilateral. The cortical hypertony is a true uterine or uterotubal reflex. The authors have shown similar changes during tubal insufflation.

J. P. GREENHILL.

**Fernandez, J. H.:** Hysterectomy As Treatment of Complete Genital Prolapse, *Obst. y ginec. Latine Am.* 3: 265-270, 1945.

For the treatment of complete prolapse of the uterus the author recommends supravaginal hysterectomy combined with fixation of the cervical stump to the abdominal wall. For this combined operation he proposes the name hysterectopexy. He believes this operation corrects the anatomic relationships, even though the prolapsed tissues are replaced in an exaggerated degree.

J. P. GREENHILL.

### Labor: Management, Complications, etc.

**de Gouvea, L. R. L.:** Considerations of Laceration of the Perineum and Episiotomy, *Arch. brasil de méd.* 35: 155-160, 1945.

The author reviews the literature on perineal lacerations and its treatment. He also studied the literature concerning episiotomy, and points out that Ould was the first to employ episiotomy in 1742 and not Michaelis in 1810, as generally believed. de Gouvea discusses the various types of episiotomy and concludes that the mediolateral or diagonal incision is the one which offers the greatest advantages. It does not matter whether the incision is made on the right or the left side. The author prefers the left side. He emphasizes that in order to insure the full benefit of an episiotomy it must be made early but not too early. The repair must be an anatomic one, layer by layer.

J. P. GREENHILL.

**de Gouvea, L. R. L.:** Transverse Presentation, *Arch. brasil de méd.* 35: 239-266, 1945.

The author presents a detailed study of the subject of transverse presentation. At the Carlos Chagas Hospital the incidence of shoulder presentation was 0.64 per cent in single pregnancies, and 5.3 per cent for the second fetus in cases of twin pregnancies.

## Correspondence

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### Adrenal-Like Ovarian Tumor

*To the Editor:*

I should like to comment on an article written by Dr. Arthur H. Curtis in the July issue of the JOURNAL 52: 115, 1946, entitled "The Origin of Adrenal-Like Tumor of the Ovary." On page 120 Dr. Curtis writes: "Also, if adrenal rests do give rise to adrenal-like tumors of the ovary, it is strange that adrenal rests are rarely, if ever, demonstrable in the ovary."

I want to take issue with this statement. During my year as resident in pathology in the Department of Obstetrics and Gynecology at Bellevue Hospital, I became interested in fetal ovaries and routinely took sections of the ovary whenever I autopsied a female infant. On one occasion, a section through the hilum of an ovary obtained from a term female stillborn revealed an adrenal rest. Histologically, it resembled the adrenal cortex. I showed it to Dr. William E. Studdiford, Jr., who at that time was director of the department, and he commented that this was not a rare finding, and that he had seen adrenal rests on a number of occasions.

I wonder if anyone else would care to comment on this statement by Dr. Curtis?

GEORGE SPECK, M.D.

AUGUST 7, 1946

2806 SOUTH RANDOLPH STREET  
ARLINGTON, VA.

### Reply by Dr. Curtis

*To the Editor:*

Robert Meyer told me that John Miller has made the most exhaustive and dependable survey of the world's literature on ovarian tumors. Miller states (Lubarsch-Henke, VII<sup>3</sup>, 752, 1937) that adrenal elements in the ovary itself occur rarely, if ever, with certainty. Usually there is confusion with corpora atretica.

Robert Meyer (Arch. f. Gynäk 145: 2, 1931) records the accidental finding of an adrenal rest in the cortex of the normal ovary of a four-month fetus; he states, "Most arise in the ligament and include the ovary secondarily."

Saphir (AM. J. OBST. & GYN. 37: 1008, 1939), among three objections to the adrenal rest theory of origin of so-called lutein-cell tumors, emphasizes the rarity of adrenal rests in the ovary.

Walter Schiller has been repeatedly quoted to have found a frequent incidence of adrenal rests in infant ovaries. Dr. Schiller informed me that such is not the case, that he agrees with the belief that adrenal rests in the ovary are exceedingly rare, and that he is in accord with the general belief that nearly all adrenal rests of the genitals are in the broad ligament or hilum of the ovary, rarely, if ever, in the ovary itself. Incidentally, Schiller has seen our so-called adrenal-like tumor of the ovary and agrees with me regarding its origin.

It will be noted that Dr. Speck's tumor was purported to have been present in a section through the hilum of the ovary, not in the ovary itself.

ARTHUR H. CURTIS, M.D.

SEPTEMBER 12, 1946

303 EAST SUPERIOR STREET  
CHICAGO, ILL.

## Necrology

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**J**OHAN ALBERTSON SAMPSON, M.D., teacher, author, and a member of the Advisory Editorial Board of the JOURNAL since its founding, died in Albany, December 23, at the age of 75 years. A graduate of Williams College and Johns Hopkins, he came to Albany in 1905, was senior gynecologist at the Albany Hospital since 1937, and Professor of Gynecology at the Albany Medical College. Dr. Sampson was the author of many meticulously written and illustrated papers, dealing principally with research into endometriosis and its associated problems. He was a Fellow and past President of the American Gynecological Society. Born near Troy, New York, he spent his entire professional life in its vicinity, never married, and, aside from his outstanding professional attainments, devoted himself to the raising of trees as a hobby. Quiet, reserved, a scientist in manner and ambition, his researches and attainments were widely recognized.

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**H**OWARD FRANCIS KANE, A.B., M.D., of Washington, D. C., died on July 21, 1946, at his birthplace and final home in Machias, Maine, at the age of 59 years. A graduate of Bowdoin and the George Washington School of Medicine, he became instructor and later Professor of Obstetrics and Gynecology at his Alma Mater, and attending obstetrician at the University, Gallinger, and Garfield Hospitals. During World War I he served with the British Expeditionary Force, was captured by the Germans, interned for six months as a prisoner, received the British Military Cross, and was discharged as a major in the Medical Reserve Corps. In World War II he was made a Commander in the United States Naval Reserve, and was subsequently appointed Chief of the Obstetrical Division of the United States Naval Hospital at San Diego. A member of many medical societies, Diplomate of the Board, an active practitioner in his special field, a foremost teacher, a frequent writer of articles for medical journals, and an excellent speaker, Dr. Kane was closely identified with the development of paraldehyde analgesia in labor and the resuscitation of the newborn.

## Items

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### **The International Congress of Obstetrics and Gynecology**

The Congress will be held in Dublin, Ireland, during the week beginning July 7, 1947, to celebrate the Bicentenary of the Rotunda Hospital. Representatives from all parts of the world have signified their intention to participate in the presentation of an elaborate program which includes addresses and discussions on the history of midwifery, puerperal sepsis, eclampsia, sterility, puerperal mortality, and obstetric shock. Messrs. Thomas Cook and Son, Ltd., are the authorized travel agency and also accept registrations for the Congress. The Honorary Secretary is Mr. G. F. Klingner, Rotunda Hospital, Dublin. The tentative program will be published in the February issue.

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### **The American Board of Obstetrics and Gynecology**

#### **Examinations**

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 7, 1947.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held June 1 to 7, 1947, at Pittsburgh, Pa. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pa.

PAUL TITUS, M.D.

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The following physicians are to be included in the list of diplomates certified by the American Board of Obstetrics and Gynecology: Dr. Martin Clyman, 285 Central Park West, New York, N. Y.; Dr. Owen C. Mullaney, 99 Bay State Road, Boston, Mass.

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### **The Central Association of Obstetricians and Gynecologists**

The Association offers two annual prizes of one hundred dollars each, one to be awarded for the best investigative, the other for the best clinical presentation in the field of obstetrics and/or gynecology submitted by any accredited physician, research worker, or medical student within the confines of the Association.

For further information apply to Dr. John I. Brewer, Secretary, 104 South Michigan Avenue, Chicago, Ill.

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#### **Erratum**

In the discussion by Dr. H. B. Matthews on the "Clinical Evaluation of Ectopic Pregnancy" in the October issue of the JOURNAL on page 554, in line 22, the sentence beginning "Nowdays without better equipment," should read "Nowadays with our better equipment." In paragraph five, line 11, instead of "2,000 c.c. of fluid," this should read "2,000 c.c. of blood."

## Vaginal Lacerations Resulting From Coitus

*To the Editor:*

Publication of the case report by Dr. Nicholls, which appeared on page 500 of the September, 1946, issue of the JOURNAL, under the title "Rupture of the Posterior Vagina During Normal Coitus," is taken as an indication of the infrequency of this type of accident. I am therefore prompted to communicate my experience with three similar cases, all of which occurred within a recent period of two months.

CASE 1.—I. G., single, white, aged 20 years, was admitted to Roosevelt Hospital at 12:30 A.M. on July 17, 1946, complaining of vaginal bleeding. At 10:00 P.M., two and one-half hours earlier, while having coitus, she experienced a sudden severe pain deep in her vagina "as though something were bursting," promptly began to bleed from the vagina, and soaked 15 perineal pads and two towels prior to admission. Two months previously she had had a spontaneous delivery of a baby weighing 8 pounds 2 ounces, at which time "a number of stitches were taken." This was her first sexual experience since then. On admission, the patient was in shock, with a blood pressure of 80/40, pulse 120, vomiting, and complaining of thirst. A ragged vaginal laceration about 5 cm. in length was found just posterior to, and to the right of, the cervix, extending through the mucosa and underlying fascia, but not involving the peritoneum. A blood transfusion was given and the laceration was repaired with catgut sutures, under pentothal anesthesia. Convalescence and healing were uneventful.

CASE 2.—Just eight days later, on July 25, 1946, another patient, M. W., 28 years of age, single, white, was brought to the accident room three hours after having had intercourse—for the first time, according to the patient. Although not complaining of pain, she began to bleed "in spurts" immediately after coitus, and soaked 10 perineal pads prior to admission. Her blood pressure was 120/80, pulse 100, hemoglobin 10.6 grams. A 3 cm. laceration of the mucosa high in the right vaginal vault was still bleeding. Immediate repair was performed under pentothal anesthesia. Convalescence was uncomplicated.

CASE 3.—This patient, M. B., white, single, aged 24 years, was admitted to the hospital on Sept. 20, 1946, forty minutes after feeling a sudden pain during intercourse. She had had coitus with the same man several times previously. On admission, the patient complained of faintness, thirst, and lower abdominal pain, in addition to the vaginal bleeding, which was rather brisk. Her blood pressure was 135/84, pulse 116, hemoglobin 10.2 grams. A ragged tear, about 4 cm. long, encircled the posterior aspect of the cervix, extending through the vaginal mucosa but not into the cul-de-sac. This rent was repaired under pentothal anesthesia, and the patient left the hospital two days later.

The relative infrequency of lacerations of the vaginal vault among adult women as a result of normal coitus is attested by our hospital records, among which only two similar cases could be found during the past five years.

HAROLD SPEERT, M.D.

THE ROOSEVELT HOSPITAL  
NEW YORK CITY  
Oct. 12, 1946.

- St. Louis Gynecological Society.** (1924) *President*, Otto Krebs. *Secretary*, John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society.** (1944) *President*, Wynne M. Silber-nagel. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Harry Gordon. *Secretary-Treasurer*, J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, H. H. Gibson. *Secretary*, Alven M. Weil, 1030 First Central Tower Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology.** *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.



# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society. (1876) *President*, Norris Vaux, Philadelphia, Pa. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists. (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, Chicago, Ill. Annual meeting Louisville, Ky., October 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists. (1938) *President*, Robert A. Ross, Durham, S. C. *Secretary*, T. J. Williams, University, Va. Annual meeting at the General Oglethorpe Hotel, Savannah, Ga., Feb. 7-8, 1947.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, Alice F. Maxwell, San Francisco, Calif. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas, Tex. Annual meeting Atlantic City, June, 1947.
- New York Obstetrical Society. (1863) *President*, Harvey B. Matthews. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. (1868) *President*, F. Sidney Dunn. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. (1878) *President*, Ralph A. Reis. *Secretary*, Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society. (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Charles Hunt. *Secretary-Treasurer*, Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. (1934) *President*, Charles J. Barone. *Secretary*, Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. (1861) *President*, George Van S. Smith. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society. (1931) *President*, Goodrich C. Schaffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society. (1933) *President*, James R. Costello. *Secretary*, Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society. (1924) *President*, Eugene H. Counties. *Secretary*, Joseph W. Reddick, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

double importance: (1) they may cross the placental barrier to the fetal circulation causing a reaction with the fetal red cells and the production of hemolytic disease; or, (2) if the sensitized mother is given a transfusion of Rh-positive blood, a severe hemolytic reaction occurs. It appears that over 90 per cent of hemolytic disease may be explained on this basis, and that the remainder may be attributed to other blood characters such as A, B, Hr, etc. For further details the reader is referred to the papers of Potter (1943) and Diamond (1945), who have published comprehensive reviews of the subject covering the available literature.

Early difficulties with nomenclature, antisera, and laboratory techniques served only to confuse the clinician. Consequently, the Rh antigen for some time was almost "a laboratory baby." Many laboratory reports were highly technical, and from the clinical side there repeatedly appeared reports of isolated cases from which hasty conclusions were drawn based on insufficient laboratory and clinical evidence.

Gradually supplies have become available, techniques have been given approval, and the nomenclature has been stabilized. So that now it remains for us to evaluate standardized studies of large numbers of patients, and these studies may support the theories that have been advanced. Soon we may hope to discover a method of avoiding hemolytic disease, or at least a better method of treating the condition.

### The Development of a Clinic Policy

In late 1943 our supply of Rh testing serum was pitifully small. It was necessary to limit examinations to those women who gave a past obstetric history which indicated that they had previously given birth to an infant that evidenced hemolytic disease. Our chief concern was the possibility of transfusion reaction should any of these patients later need blood. In June, 1944, our first post-transfusion death occurred which could be definitely traced to Rh incompatibility (Case 3). Fortunately, soon after this (August, 1944), a liberal quantity of testing serum, as well as laboratory facilities for unlimited determinations of Rh type and antititer, became available to us. We immediately adopted the following policy:

1. All clinic patients were Rh typed at the first clinic visit.
2. As far as possible, the husbands of all Rh-negative patients were typed.
3. Beginning about the thirty-sixth week, all Rh-negative patients were to have weekly anti-Rh determinations performed. (We have since changed this procedure to the thirty-seventh week.)
4. Any patient in whom Rh antibodies had been demonstrated was re-evaluated on admission to the hospital in labor. Type O, Rh-negative blood was put in readiness for mother or for infant. Preparations were made to study samples of cord blood with regard to Rh type, hemoglobin, and the presence of erythroblasts. These studies were done at six-hour intervals on the newborn infant. In addition, the infants were not allowed to breast feed. The placenta was studied both macroscopically and microscopically for evidence of hemolytic disease.
5. The infants of many Rh-negative women who did not have demonstrable antibodies were also studied with daily hemoglobin determinations and blood smears for periods of about three days. In addition, the placentas were examined microscopically. (We have since abandoned these examinations, as will be explained later.)
6. Throughout the clinic, only Rh-negative blood was to be given to Rh-negative patients.

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## Original Communications

### THE APPLICATION OF OUR KNOWLEDGE OF THE RH FACTOR

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IN THE space of a little over five years, the Rh factor has risen from a position of laboratory obscurity to a subject of definite clinical importance. In this short time theories were swiftly advanced and just as quickly proved or disproved by clinical experience and further investigation. This evolution was so rapid that almost immediately it became difficult for the busy clinician to keep pace with the fast-changing terminology and the latest theories and their application. Yet in the early period of the Rh study, its implications in the field of obstetrics were realized. Consequently, late in 1943, the author was assigned the problem of keeping abreast of the literature, and, with the available material, of adopting measures which could be applied on a large scale at the Woman's Clinic of the New York Hospital.

It is the purpose of this paper to trace the changes in clinic policy as our knowledge increased and Rh testing materials became available. The statistics of almost 5,000 Rh determinations will be analyzed and a few interesting cases and observations discussed. We may say at this point that several tragic and near-tragic errors were made; on the other hand, many more were avoided. Two transfusion deaths resulting from Rh incompatibility will be reported.

#### The Rh Theory

There has been much written about the Rh blood group. In six years, over 300 articles have appeared. The history and theories of the Rh antigen and the development of its clinical aspects have been reviewed many times. Typically, an Rh-negative female bearing an Rh-positive fetus (the positivity inherited from an Rh positive father) may, during the course of pregnancy, be exposed to Rh antigenic substance which passes across the placental barrier from the fetus. The mother is therefore stimulated to produce Rh antibodies, and she is then considered sensitized to Rh. Again, the mother may have been sensitized by a transfusion of Rh-positive blood given prior to pregnancy. These antibodies are of

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that did not develop hemolytic disease, some proved to be Rh negative, indicating a heterozygous father. In one case the maternal antibodies were developed as a result of previous transfusions, for mother, father, and infant were all Rh negative and of the same blood group. In other cases studies were incomplete. But the interesting observation remains that by discovering antibodies in the maternal blood we were able to place 55 infants under observation for the presence or the development of hemolytic disease, and all but two of our 36 cases of hemolytic disease during this period of time occurred in the 55 suspected cases.

Should the antibody titer of a patient suddenly rise late in pregnancy, and a viable fetus is assured, some writers have advocated immediate delivery by the induction of premature labor or by cesarean section. Our one experience with this recommendation may be presented.

CASE 1.—The patient was a 29-year-old, para v, gravida ix, one living child. Her past obstetric history was typical, and showed that she had borne jaundiced and hydropic infants. Initial blood studies showed the patient to be group O, Rh negative, her husband to be group B, Rh positive, and the one living child to be group B, Rh positive.

Beginning at the seventh month of gestation, repeated determinations were performed at frequent intervals in an attempt to demonstrate antibodies. On September 26 and October 1, no antibodies were present, but on October 8 antibodies were demonstrated. At this point the fetus was estimated to weigh 2,300 Gm., the fetal heart was of good quality, and an x-ray revealed no gross abnormalities. A medical induction of labor was unsuccessful. On October 13, 1945, with the patient entering her thirty-fifth week of pregnancy, a cesarean section was performed without difficulty. The amniotic fluid was golden yellow and the fetus was a typical hydropic infant of 2,360 grams. The infant promptly expired. Examination of the cord blood showed the infant to be group B, Rh positive. A smear revealed 25 per cent erythroblasts. The hemoglobin was 6.5 grams. The placenta weighed 1,320 Gm., and both macroscopically and microscopically presented the usual findings associated with hydrops.

It is probably still too early to recommend or condemn early delivery in the face of a rising antititer. Certainly in this case, the mother was subjected to undue risk, and the results were extremely discouraging.

Therapeutic Abortion

Sanctioning Rh negativity or a past obstetric history of hemolytic disease in previous infants as an indication for therapeutic abortion is fraught with danger, and we have had no experience in this direction. At present too many individuals are ill informed or misinformed concerning the Rh antigen to advocate such a procedure.

TABLE II. LABORATORY STUDIES OF A PATIENT SURVIVING A TRANSFUSION REACTION AS THE RESULT OF RH INCOMPATIBILITY

DAY POST-TRANSFUSION	CO <sub>2</sub>	NPN	ICTERIC INDEX	NITROGEN UREA	UREA CLEARANCE	PSP TEST
4	43	50	6.0	--	19%	30%
5	43	54	8.5	37	--	--
8	47	54	--	33	33%	35%
9	43	43	--	30	--	--
10	47	47	--	32	--	--
11	44	47	--	--	--	--
12	49	44	--	--	--	--
17	51	37	--	--	49%	--

### Results of the Study

The study includes approximately 5,000 Rh determinations. Practically all of the patients were white (3.8 per cent Negro). Repeated samples of the series show 86 per cent of those tested to be Rh positive, and 14 per cent to be Rh negative.

During the past three years, the incidence of proved hemolytic disease at the Woman's Clinic of the New York Hospital has been 1:230 full-term and premature deliveries. These figures may be compared with those of Javert, who, in 1942, reported our clinic incidence as 1:438 for the five-year period from 1936 to 1941. Today many more cases are being diagnosed, as may be noted from Table I which is based on Javert's previous report of cases through 1941, and our own cases from 1942 through 1946.

TABLE I. INCIDENCE OF HEMOLYTIC DISEASE

YEARS	CASES	DELIVERIES	RATIO
1933-1936	7	10,819	1:1545
<i>First Five-Year Study:</i>			
1936	8	3,390	
1937	9	3,443	
1938	8	3,032	1:438
1939	7	3,383	
1940 (twins, one pair)	9	3,672	
Five-Year Total	41	17,520	
<i>Second Five-Year Study:</i>			
1941	7	3,504	
1942	6	3,195	
1943	10	3,302	1:384
1944	8	3,292	
1945	12	3,241	
Second Five-Year Total	43	16,534	
<i>Third Five-Year Study:</i>			
1946	24	3,603	
Grand Total	115	48,476	

Some authors report hemolytic disease to be much more common than we have indicated. It is our belief that many are too eager to make the diagnosis of hemolytic disease of the newborn without sufficient laboratory and clinical evidence to substantiate the impression. In the future, as some writers have already suggested, the use of the term hemolytic disease of the newborn should be confined to those conditions which are the direct result of incompatibility of maternal and fetal bloods. Hemolytic disease closely resembles other conditions, and we must for the present depend on the laboratory findings in a large part. On the possibility that we might be overlooking so-called "subclinical forms" of hemolytic disease, for the past year and a half we have been performing hemoglobin determinations and blood smear studies on the newborn infants of many Rh-negative mothers in whom antibodies were not demonstrable. In addition, the placentas were examined microscopically. We have now abandoned this work, for the placentas have appeared normal and there has been no evidence that the blood studies of the infants varied from the normal.

Our most interesting finding was that almost all of our cases of hemolytic disease occurred in infants whose mothers had demonstrable antibodies in their blood.

### Rh Antibodies

In the past years we have delivered 55 patients with antibodies present in their blood. All but two of our 36 cases of hemolytic disease occurred in this group. Nineteen infants showed no evidence of the disease. Of these infants

CASE 4.—The patient was a 32-year-old, para iii, gravida vi, who was admitted to the obstetric service in 1944. Her obstetric history revealed three normal deliveries prior to the delivery of a deadborn, macerated, erythroblastotic (?) fetus at six months in 1940. At delivery the patient suffered a blood loss of 800 c.e. and a transfusion of supposed compatible blood was given. Shortly after the transfusion was completed, a reaction occurred which was characterized by chills, fever to 39.2° C., and shock. On the day following the transfusion there was an icteric tint to the sclera and skin, and it was noted that the patient had not voided since delivery. Catheterization yielded but 10 c.e. of urine. Determination of the patient's Rh type showed her to be Rh negative, while the donor was Rh positive. The patient did not respond to the usual methods of treatment, and on the tenth post-transfusion day she went into extremis and expired.

*Discussion.*—It is apparent in this case that the renal shutdown occurred as the result of an Rh-negative individual being transfused with Rh-positive blood, and that the accident would have been avoided had the patient been Rh typed prior to transfusion. The patient had been sensitized by previous pregnancies, for she had no history of previous transfusion therapy.

CASE 5.—The patient was a 33-year-old, para iii, gravida iv. There was no positive history of hemolytic disease. Her blood was typed as group A and Rh positive. An anemia was present which did not respond to the usual therapy, so that admission to the hospital in the thirty-ninth week of pregnancy was advised, and a transfusion of 500 c.c. of group A, Rh positive, supposedly compatible blood was administered. There was no reaction until approximately two hours after the discontinuance of the transfusion, at which time the patient complained of chilly sensation, became nauseated, and vomited. Soon after this she began to talk incoherently, and her face became markedly flushed. No icterus was demonstrable. On the evening of the first post-transfusion day, 20 c.e. of dark brown urine was passed which was guaiac positive for blood. By the second post-transfusion day the patient had passed a total of 70 c.c. of urine. The blood bank then rechecked the Rh of the patient and found her, contrary to their initial report, to be Rh negative. Appropriate therapy was instituted, but after showing marked clinical improvement fifteen days post transfusion the patient suddenly expired.

*Discussion.*—This patient was sensitized by pregnancy and the reaction was due to Rh incompatibility. Blood drawn on the third post-transfusion day for antititer determination showed that the "serum does not contain any blocking antibodies, and the test with serum suspended cells is negative. Presumably this may be due to the so-called negative phase of iso-immunization, and it can be expected that in a week or ten days antibodies will be demonstrable." A blood specimen drawn 10 days post transfusion showed that the "serum was weakly positive for blocking antibodies with a questionable reaction to serum suspended cells." Another qualified examiner reported this same specimen to contain "anti-Rh agglutinins of the hyperimmune type or blocking variety which is consistent with a transfusion of incompatible blood." The error in typing was due to testing serum of poor specificity employed at that time.

### Infant Mortality

In hemolytic disease of the newborn it is often difficult to subdivide the individual case into jaundiced, hydropic, or anemic form, for many times there is overlapping. Javert reported the infant mortality figures for the Woman's Clinic in 1942, and to his original report may be added our own figures, shown in Table III. Table IV compares the type of hemolytic disease with the mortality.

## Recovery Following Transfusion of Incompatible Rh Blood

Since the adoption of the above-outlined policy almost two years ago, three major transfusion reactions have occurred. Two of these patients survived, and their case records may be described.

**CASE 2.**—The patient was a 38-year-old, para iv, gravida v, who was delivered on January 3, 1944, without incident. Her past history was not remarkable but for a single transfusion which had been given twelve years before the present admission. On the eighth postpartum day, because of a persistent anemia, the patient was typed as group O, Rh negative, and was inadvertently given 200 c.c. of pooled red cells in suspension. At this point a severe transfusion reaction occurred which was marked by chill, fever of  $38.8^{\circ}\text{C}$ ., shock, and air hunger. The patient was immediately given 500 c.c. of M/6 lactate, and the symptoms rapidly subsided in a matter of a few hours. A sample of blood drawn five hours post transfusion showed a low anti-Rh titer, and the reaction to have been hemolytic in nature. The urinary findings were not remarkable, and the output remained good.

*Discussion.*—This Rh-negative patient was sensitized either by the previous transfusion or by pregnaneies. It was an error to have given pooled red cells, the larger proportion of which were certainly Rh positive.

**CASE 3.**—The patient was a 31-year-old, para vi, gravida vii, whose obstetric history showed the fourth infant to have been jaundiced, and the sixth to have been deadborn. The patient was known to be Rh negative and her husband to be Rh positive. Because of anemia, a transfusion of supposed Rh-negative blood was started soon after delivery. After 250 c.c. of blood had been administered, chills and fever of  $39.5^{\circ}\text{C}$ . ensued. A recheck of the donor's blood showed it to be Rh positive. The patient had previously been alkalinized. During the next twenty-four hours the output of urine was 125 c.c., but thereafter it was quite adequate. On the third postpartum day investigation showed the spleen to be two fingerbreadths below the costal margin and the liver to be four fingerbreadths below the costal margin. Repeated urine examinations showed an inability to concentrate beyond 1.008. Detailed studies are presented in Table II. By the seventh postpartum day the patient was asymptomatic, and during the following two weeks the splenomegaly and hepatomegaly slowly disappeared. On May 24, 1946, the patient was found to be group A, Rh negative, and the serum showed the presence of strong blocking antibodies. The specific gravity of the urine was 1.025.

*Discussion.*—This case illustrates a major laboratory error in mistyping the donor blood. Although total urinary output was reduced only during the first twenty-four hours post transfusion, the urinary function studies indicate that kidney damage was profound, but that the insult was temporary in nature and recovery relatively rapid. It may be of importance that the patient had been alkalinized prior to transfusion.

## Transfusion Deaths Due to Incompatible Rh Blood

As has previously been noted, we have observed and studied two patients whose deaths could be directly attributed to transfusion with incompatible Rh blood. The first of these (Case 4) occurred prior to the development of a definite clinical policy. Both are of such importance that they will be discussed in detail by Williams.



x-ray studies of the fetus in an effort to demonstrate halo formation or the Buddha position characteristic of certain types of hemolytic disease.

Our present-day knowledge has led us to close observance of the patient in labor who has had antibodies demonstrated in her blood during the antenatal course. Routinely, Rh negative, O blood is made ready for possible transfusion or a profoundly anemic infant. Cord blood samples are taken for determination of the infant hemoglobin and Rh type as well as a smear study of cord blood. The placenta is inspected, weighed, and microscopic sections taken in an effort to aid the making of the diagnosis. Close attention is paid to the presence of hydramnios and discolored amniotic fluid. At birth the infant is examined closely for any evidence of hemolytic disease, and, if it is apparent that it is present, the infant is immediately transferred to the pediatric service for appropriate care. If the infant appears quite normal, hemoglobin determinations and smear examinations of the infant's blood are performed at six-hour intervals in order to detect any change at the earliest possible moment.

The husband's parents and all available children are Rh typed when an infant develops the disease. In this way we are in the best possible position for prognosticating the outcome of future pregnancies. On several occasions we have been able to show the father to be heterozygous Rh positive, and were thus able to offer the couple at least a fifty-fifty chance regarding further pregnancies.

The two transfusion deaths were most unfortunate. They have been presented in the hope that others may avoid such mishaps, and that a more satisfactory method of treatment may soon be found for transfusion accidents such as these.

The fetal mortality remains high. At present the hydropic form of hemolytic disease seems to be without a means of treatment. No one has been able to desensitize a woman or prevent sensitization, although Homburger's recent work may prove the initial step in the right direction. At birth, the infant is often dead or malformed and in critical condition. We should be able to reduce materially the mortality figures of the anemic form of hemolytic disease if care is exercised in making a prompt diagnosis and in administering Rh-negative blood in sufficient quantity. The jaundice type of the disease offers a real challenge. So far, in cases of this type, we have used the hemoglobin and erythrocyte levels as an index for when transfusion was indicated. The results have been discouraging. If the infant is severely jaundiced and permanent central nervous system damage is quite probable, very little can be done. However, in those infants who present a minimal jaundice at birth, exsanguinating transfusion, although presenting some technical difficulties, may be the temporary answer to the problem.

If further studies such as ours indicate that the Rh-positive infant of a woman who has demonstrable antibodies in her blood is to develop hemolytic disease, no matter what the appearance of the infant at birth, exsanguinating transfusion soon after delivery may reduce fetal mortality. It is here that the obstetrician stands in a particularly strategic position, for prompt action may be lifesaving. It is a well-known observation that many infants which appear normal at birth, in a matter of hours, or a few days at the most, may develop



TABLE III. FETAL MORTALITY IN HEMOLYTIC DISEASE OF THE NEWBORN

YEARS	CASES	MORTALITY	
		NUMBER	PER CENT
1933-1936	7	6	85
1936-1940	41	29	71
1941-1945	43	24	56
1946	24	10	42

TABLE IV. THE TYPES OF HEMOLYTIC DISEASE IN RELATION TO FETAL MORTALITY

TYPE	CASES	DEATHS	FETAL MORTALITY (%)
Hydropic	32	32	100
Jaundiced	49	21	43
Anemic	13	3	23
Hemorrhagic diathesis	4	1	25
Unclassified	4	4	100
Total	102	61	60

Prompt and sufficient transfusions of Rh-negative blood, although of aid, are not the complete answer to the problem of treating the infant with hemolytic disease. Many of the infants die, even though the hemoglobin and erythrocyte count are maintained at a high level. These infants apparently succumb to the accumulation of waste products of their own blood destruction. In these cases, exsanguinating transfusions have been suggested, but few have tried this therapy.

### Discussion

The importance of determining the Rh type of all antenatal patients has been clearly demonstrated at the Woman's Clinic of the New York Hospital on many occasions. When an obstetric emergency arises and large volumes of blood must be given immediately and rapidly, it is indeed satisfying to have predetermined the Rh blood type and thereby obviate the delay which would otherwise be necessary before a transfusion of whole blood could safely be given.

The importance of testing for Rh antibodies has been indicated. Our studies have shown the tests to be of value in predicting with a high degree of accuracy the outcome for the infant, and they have made us better prepared to treat promptly the newborn infant who develops hemolytic disease. Several of our cases have shown that antibodies may develop in ten days; therefore, it is our present policy to draw blood for antibody determinations on all Rh-negative patients at weekly intervals beginning with the thirty-seventh week of gestation. A patient who gives a definite history of having borne infants with hemolytic disease has antititers prior to the thirty-seventh week, for we have found that in these patients the fetus may die in utero as early as the twenty-fourth week of pregnancy.

In addition, if for some obstetric reason cesarean section is being entertained as the method of delivery for a patient who has demonstrable antibodies, it should be borne in mind that the studies here presented indicate that about 60 per cent of the infants delivered of such mothers develop hemolytic disease. Before a final decision as to type of delivery is made, it would be wise to obtain

# MASCULINIZING TUMOR OF THE OVARY OF THE ADRENAL TYPE

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THE phenomenon of sexual metamorphosis in adult life is always a dramatic event, and of striking interest to layman and scientist alike. The demonstration that such Jekyll and Hyde mutations may be dependent upon a tumor no larger than a pea and are even reversible following ablation of the tumor, has a definite appeal to the imagination.

The attention of clinical pathologists has been focused upon this group of tumors—the disgerminoma granulosa cell and arrhenoblastoma tumors which have excited widespread interest since Robert Meyer's classical work was presented before the American Gynecological Society in 1931. To these may be added the Brenner tumor, theca-cell tumor, luteoma, and mesonephroma, or adrenal tumor (masculinovoblastoma), some of which have been associated in some degree with these striking phenomena.

Reis and Saphir have classified true masculinizing tumors as:

1. Arrhenoblastoma originating in male-directed sex cells persisting in the ovary from the early stages of gonadogenesis.
2. Disgerminoma arising from early gonadal cells before they acquired their power of specific sex direction.
3. Hypernephroma, interrenalism, or Gravitz tumor, adrenal rests or adenomas (Novak) misplaced within the ovary.
4. Luteomas with their disputed identity.

Clinically, however, the full flower of masculinization seems to appear in the groups of arrhenoblastomas and adrenal tumors, and in Karsner's dictum: "In spite of the lack of convincing evidence, it is probable that the beard, general hirsutism, male conformation, enlarged larynx, and elitoris are due to male sex hormone." However, in repeated cases of undoubted masculinization the demonstration of excreted androgens in increased amounts has not been constant and, as stated by Novak, we probably do not understand many of the factors underlying sex differentiation.

The factors involved in the relationship between the gonads and the adrenal cortex, close relatives embryologically, are not well known. Lesions in both the ovarian medulla and adrenal cortex produce masculinization in women which may be consonant with the Bauer hypothesis that adrenal tumors tend to masculinize the female and feminize the male, i.e., support the characters of the opposite sex. As proof of this perverse reaction, Schiller states he has seen two cases of adrenal-like testicular tumors associated with feminization in the male.

The relationship of the dubious luteomas to this group of tumors, i.e., the adrenal-like tumor of the ovary, is still most obscure and confused, especially

the jaundice or anemie type of hemolytic disease. By being able to predict such an outcome, the precious hours between birth and the development of the disease may be used to replace, or partially replace, the newborn infant's blood with Rh-negative blood. Theoretically at least, hemolytic disease might thus be avoided or reduced in severity.

In some cases blood destruction goes on in the fetus while in utero for quite a period before birth. This is obvious in the hydropic form of the disease. Apparently the destruction in this type is so massive that the powers of regeneration cannot keep pace, the fetus dies, and the profoundly anemic, hydropic type of infant is the outcome. Such a chain of events occurs to a milder degree in the jaundice type. But what of the waste products of this blood destruction? Is it not possible that these products pass the placental barrier and are excreted by the maternal organism? Some of our recent studies tend to show this to be the case. Have the infants which appear normal at birth depended on the mother for the excretion of these products, and soon after birth they develop jaundice because they, by themselves, are unable to excrete the total products of blood destruction? We are hoping that blood chemistry studies late in pregnancy on patients with Rh antibodies may be of further prognostic aid.

The author is indebted to Doctors Philip Levine and Louis K. Diamond for determinations of anti-Rh titers, and to Dr. R. G. Stillman for his aid in this study.

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of the normal postmenopausal woman. Appearance and disappearance of the stigmas of masculinization were paralleled by the gonadotropic hormone output as determined in the urine.

### Case Report

The patient was a white woman 48 years of age complaining of pain in the back and both lower quadrants which had developed seven years previously. After two months of treatment she had become better, then pain in both lower quadrants, vaginal discharge, and low backaches developed. These symptoms persisted and gradually became worse. During the previous two years the patient noticed a loss of much scalp hair, general hypertrichosis of chest, body, and legs, and a change in her facies. Her menses began at 17 years. Periods were regular, and varied between 42 and 49 days, lasting six to seven days with profuse bleeding. She had the menopause at 37 years of age, with cessation of bleeding. She was compelled to shave her face for cosmetic reasons daily, and her voice developed a bass tone. She experienced loss of libido for the past six years. Intercourse was also painful. She had three daughters, aged 25, 27, and 28 years and had no miscarriages. Operations: appendectomy twenty-two years ago.

Physical examination: Temperature, 36.5° C.; pulse, 98; blood pressure, 150/90.

The patient was a well-developed, well-nourished, white woman, lying quietly in bed, and not appearing ill. Her facial features resembled those of a male. Chest: Large male type. Breasts: Small, soft, rather atrophic; nipples flat; no masses. Abdomen was rotund and seemed to bulge at the flanks. No definite fluid wave could be made out, although the abdomen had a dull sound to percussion. Hair: There was a marked overgrowth of hair on the face, chest, abdomen, and lower extremities. Hair on the scalp was thin and there was an area of baldness. Hair over the temporal regions was short and masculine in distribution. Extremities: Normal development and function. Hands were not stubby and fingers were not thickened. Head and face: male appearance. Voice was basso. No prognathism was present. Bridge of the nose and supraorbital regions were not unusually prominent. Urine on Jan. 20, 1942 was normal; blood was: white blood cells, 8,400; red blood cells, 6,350,000; hemoglobin, 112 per cent. Blood on Jan. 21, 1942: white blood cells, 9,000; red blood cells, 6,000,000; hemoglobin, 105 per cent.

Basal metabolic rate on Jan. 21, 1942 was -8. Wassermann was negative. Blood sugar was 85 mg. per 100 c.c. X-ray of sella and pyelograms was negative.

Operation: Perinorrhaphy, subtotal hysterectomy, bilateral salpingoophorectomy.

Pelvic examination revealed the fundus to be large, smooth, and somewhat limited in mobility. The adnexa seemed enlarged, and a definite tumor was palpable on the right. On this basis, a preoperative diagnosis of masculinizing tumor of the right ovary, presumably arrhenoblastoma, was made. The uterus was found to be in the cul-de-sac, large in size, and deeply congested. There were, however, no myomas present. The engorgement of the uterus and the deep red color were rather striking; the tubes also showed this congestion, otherwise they were normal. The left ovary was somewhat enlarged, free from adhesions. The right ovary was definitely hypertrophied, being approximately 4 cm. in its largest diameter; it was distinctly hard and presented somewhat rounded projections from its surface at a pole distant from the hilum. The ovaries were globular, light yellow in color, suggesting marked cellularity in consistency, but presenting no discrete tumor. The sur-

since progesterone itself may be androgenic. Novak is of the opinion that the luteoma, notoriously an evanescent structure, is doubtful as a source of this neoplastic growth, and it appears that most, if not all, the cases reported as masculinizing luteomas are probably of adrenal character in final analysis. He believes that the few ovarian adrenal tumors which have been observed, and also the adrenal ovarian "rests" reported by Saphir and Parker in 1936, have the structure of normal adrenal tissue, and are not of the type of the so-called hypernephroma of the ovary. There is great difficulty in distinguishing this tumor from the luteoma or thecoma, and this doubtful state is suggested in the name, masculinovoblastoma, of dubious derivation proposed for these tumors by Rottino. It is also difficult to decide whether to construe these tumors as adrenal rests or adrenal adenomas, assuming adenomas to be groups of morphologically normal, but functionally overactive cells; and Novak mentions two cases with islands of typical adrenal cells near the ovarian hilum *without masculinization*. The mere presence of such cells thus is apparently not sufficient to cause masculinization. As far as luteomas are concerned, undoubtedly many of the reported cases have been of adrenal origin, and yet in the light of the apparent close chemical relationship between progesterone and testosterone, one must at least consider the possibility of masculinization occurring from the luteomas arising from the luteinization of granulosa-cell tumors.

The weight of opinion, however, would seem to agree (Schiller) that most, if not all, of masculinizing luteomas are in reality of the adrenal type. Yet undisputed adrenal tumors in the ovary are very rare.

The arguments pro and con, and the decisions reached on morphologic grounds purely, have reached a number of stalemates with Kermauner, Saphir, and others ranged against Novak, Meyer, and Schiller.

The decision as to the identity of the tumors thus varying with the opinion of the most notable experts is obviously most unsatisfactory, yet hormonal studies systematically carried out as in the striking case (*vide infra*) have not done much to clarify the situation because the reported assays of estrogenic and androgenic substances themselves and their ratios to each other have been fraught with conflicting evidence and contradictions.

Differentiation on the basis of chemical content and ratios of cholesterol and fat content (phospholipids) and the presence or absence of reticulum (Traut and his associates) has been scarcely more fertile in establishing clear-cut identification criteria. Foehsinophil cells have been described as perhaps the underlying agency, but their definite significance is still shrouded in uncertainty. It seems obvious that only extremely careful reporting and study of this group of tumors, and the keenest analysis of them will develop a slide rule capable of giving us the answer in this nosologic confusion, with clinical manifestations, hormone assays, chemical consistency, and histologic appearance and their variational swings finally correlated.

To this conflicting state of affairs we wish to add a case occurring in a woman following the menopause which showed marked changes of masculinization and following extirpation of the tumor, reversion to the bodily habitus

the surrounding tissue on one edge, and on the opposite it blended with the adjoining tissue, and in this region the adjoining tissue was mottled light brown and pale yellow. The adjoining tissue was pale yellow and surrounded by a pinkish gray capsule.

The left ovary was pinkish yellow and had a corrugated external surface. It was firm, sectioned with moderate resistance, and the cut surface bulged slightly and was pinkish yellow. In one region the cut surface was somewhat fleshy and was pale pinkish gray. Representative sections were embedded.

Sections of the left ovary showed the stroma to be abundant, compactly arranged, and richly cellular. There were numerous corpora albicantia, and in the substance of the ovary there were many small medium sized arteries that showed intimal and medial thickening and hyalinization. There was also one small cyst that was lined with flattened epithelium, and contained some pale pink structureless material. The vessels in the surrounding connective tissue showed marked intimal proliferation with narrowing of the lumens.



Fig. 3.

Fig. 3.—Preoperative baldness and regression of hair at the crown and over the temples, i.e., masculine stigmas for the age group.



Fig. 4.

Fig. 4.—Appearance one year postoperative, showing reappearance of thick, closely growing hair on crown.

Sections of the right ovary including a portion of the tumor were stained with hematoxylin and eosin, Sudan Black, Sudan IV, and Nile blue sulfate. Stains for Fuchsinophil granules were not made. Recent observations indicated that these were probably of no important significance in the diagnosis of androgenic tissue (Karsner).

In the sections there was considerable normal ovarian stroma which was richly cellular and compactly arranged. There was also an occasional corpus albicans, and there were many small arteries showing intimal and medial thickening and hyalinization. The tumor was not encapsulated, and was mod-

faces of the ovaries were smooth, showing no trace of the atrophic pitting and scarring of the surface of a typical postmenopausal atrophy. There were no adhesions. Both kidneys were palpated and seemed to be normal in size and shape. The adrenals presented no abnormality at palpation. The gall bladder was negative for stones. Bilateral salpingoophorectomy and subtotal hysterectomy were performed.

*Pathologic Report.*—Adrenal cortical tumor of the right ovary. No pathologic diagnosis of left ovary. Focal recent hemorrhage into myometrium, atrophy of endometrium, slight chronic bilateral salpingitis.



Fig. 1.

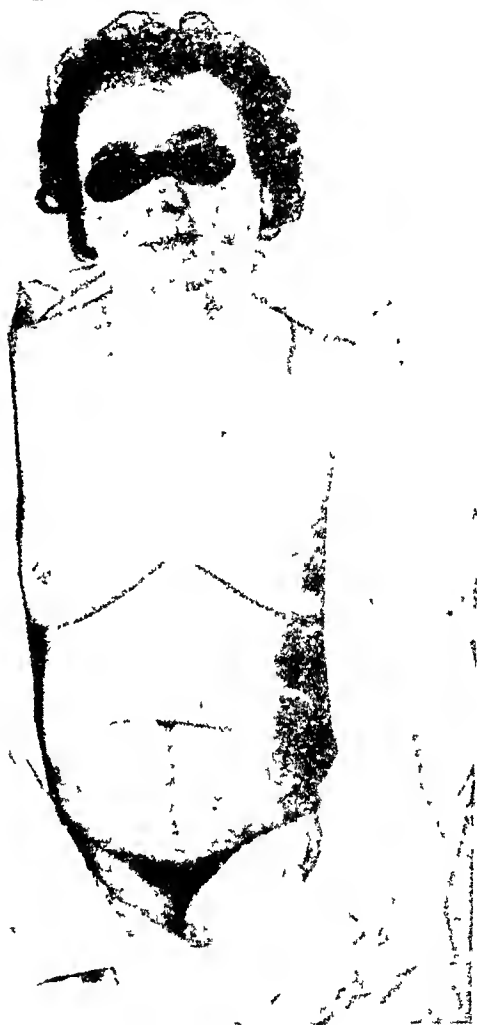


Fig. 2.

Fig. 1.—Preoperative appearance of patient. Typical hypertrichosis and masculine facies.

Fig. 2.—Appearance one year postoperative. Reappearance of feminine facies, disappearance of abnormal hirsutism. Euphoria apparent in patient's demeanor.

The left ovary weighed 5 Gm. and measured 2.7 by 2 by 1.5 cm., and the right ovary was not weighed, but it measured 3.2 by 2 by 0.9 cm. The right ovary had an external surface which was pinkish gray, corrugated, and in one region elevated. It was firm, sectioned with moderate resistance and the cut surface was slightly elevated. Near the center of the ovary there was a tumor mass which measured 1.4 by 1.2 by 0.8 cm. This tumor mass was light brown, firm, and fleshy, and its cut surface was uniformly brown, and on it there were multiple small red foci. The tumor was sharply demarcated from

Fig. 9.

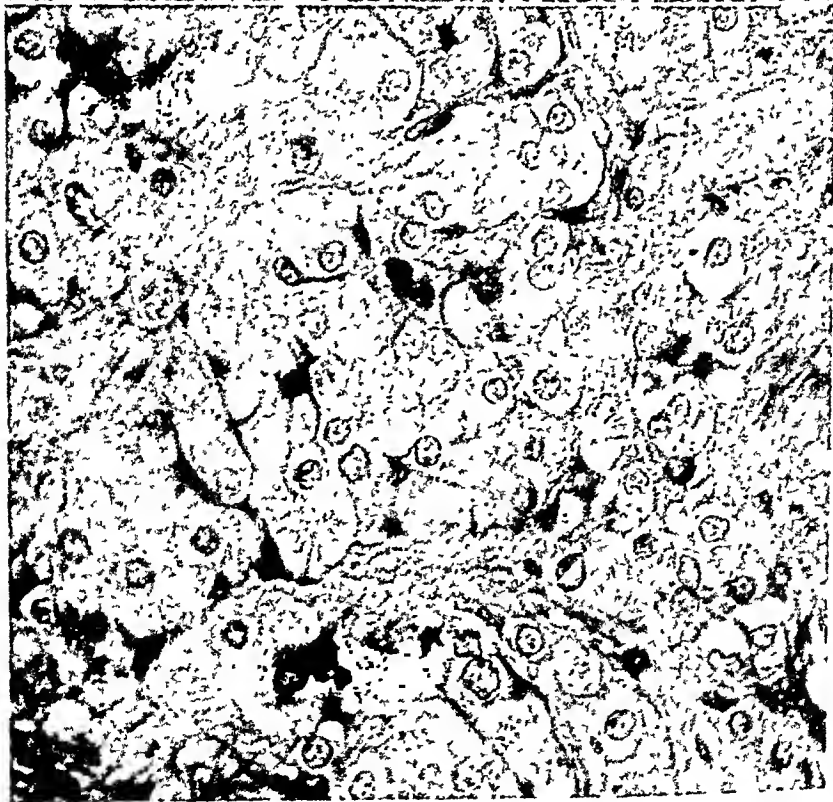
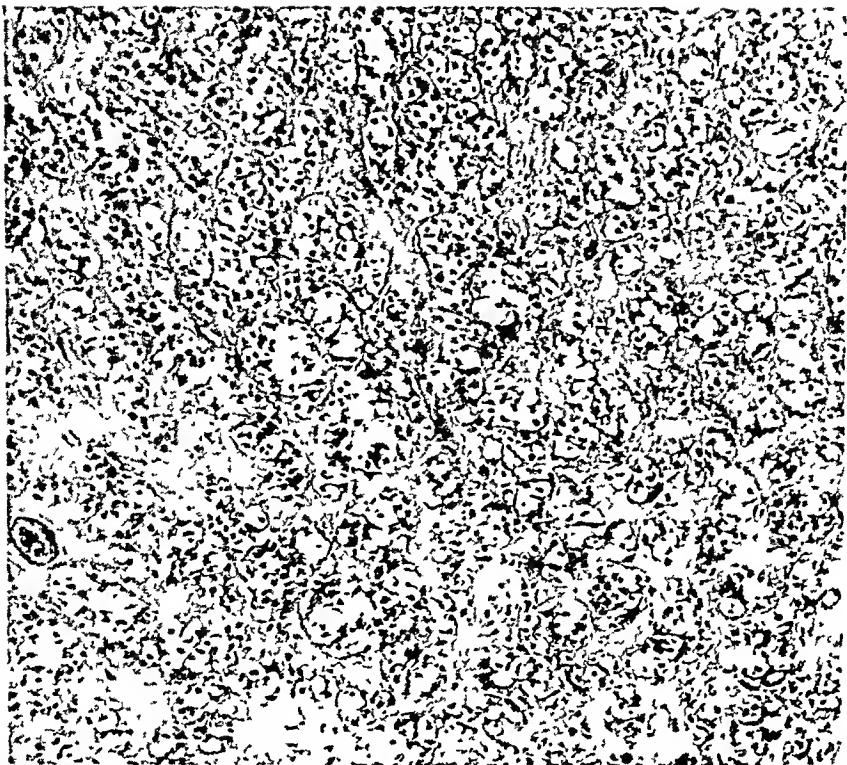


Fig. 10.

Fig. 9.—Strands of adrenal-like cells in irregular arrangement. There is no acinus or tubule formation.

Fig. 10.—High-power view showing cells resembling adrenal cells with well-defined cell boundaries.



erately cellular. The cells of the tumor were relatively large, and were for the most part cuboidal or polyhedral in outline. They had abundant pink, granular cytoplasm and relatively large circular or oval nuclei that were moderately chromatic. In many instances, the cytoplasm of the cells was



Fig. 5.



Fig. 6.

Fig. 5.—Perineum preoperative, showing hypertrichosis and hypertrophy of clitoris. (Compare size, index finger.)

Fig. 6.—Perineum, one year postoperative. Marked diminution in size of clitoris. Normal perineal hirsutism.



Fig. 7.



Fig. 8.

Fig. 7.—External surface of right ovary at operation. Approximately actual size.

Fig. 8.—Median sagittal section of right ovary, showing tumor, intrinsic in ovary. A shell of cortex is seen over the surface.

relatively clear. The tumor cells had no distinctive architectural arrangement. They were present in irregular sheets and groups, and there was no acinus or tubule formation. In general, the cells simulated those ordinarily seen in adrenal cortex. There were a few cells with large deep chromatic nuclei, but in the sections examined there were no bizarre nuclear forms or abnormal

severe symptoms, the ovaries were both enlarged to two or three times normal size and lacked the typical atrophic wrinkled and pitted appearance of the senile ovary, and were smooth and cellular-looking. The uterus was enlarged and engorged in appearance, not at all the small atrophic fibrous senile uterus of a woman ten years post menopause. This patient showed the characteristic tendency toward hypertension fairly frequent in the reported cases. The blood sugar was normal. Polycythemia was present. General appearance of the tumor suggests definite adrenal cortical cells with well-marked cell boundaries. In spite of functional behavior of the tumor in terms of 17-ketosteroids and bioassay in international units, its demonstrable output of androgens is extremely low in comparison with other reported cases, suggesting either that androgens in large amounts are not necessary to produce masculinization, or that our means of measuring them quantitatively are as yet not sufficiently refined as to be entirely reliable.

There were definite masculine stigmas of approximately two years' duration, with masculine type of baldness and recession of hair at temporal regions, rugged deeply lined facies with marked hypertrichosis of chest, abdomen, and legs, definite marked hypertrophy of the clitoris and masculine type pubic hair distribution. Complete recession of signs of masculinization and resumption of feminine habitus followed ablation of the tumor.

Acknowledgment is made to Dr. H. T. Karsner for the pathologic report, and to Drs. R. A. Shipley and R. I. Dorfman for the hormonal assays.

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mitotic figures. In the sections prepared with special stains there were numerous very small droplets of lipoidal material in the cytoplasm of many of the tumor cells.

Since operation, the scalp hair is growing short and thick. The patient believes facial hair is diminishing in amount and rapidity of growth, and definite hairless areas are appearing on the abdomen and chest. The facies shows smoothing out of wrinkles. The clitoris shows definite involution.

Follow-up of this patient over a period of two years has shown complete restitution of normal feminine facies and habitus, with scalp hair normally profuse and covering the entire crown. Facial hair, however, has been more stubborn in its persistence, and still requires shaving every third or fourth day. This, however, is not incompatible with the well-known post-menopausal tendency to general hirsutism, and generally an increase in facial hirsutism, only too often so noticeable, particularly in brunette women in the form of the feminine mustache. Body hair has completely disappeared, except for the normal feminine distribution in the normal pubic area. The anterior surface of the thighs are clear of excessive growth. The clitoris is normal in size and appearance. Pelvic examination revealed no trace of tumor.

Hormone assays were performed with the following results:

The excretion of 17-ketosteroids in the urine before operation was 11.6 mg. in twenty-four hours, and the androgen excretion as determined by bioassay was 33 international units. These values are within the normal range for adult females, and they are in contrast to the high values which are found in cases of masculinizing tumors which arise within the adrenal cortex. A number of assays made within the first week after operation yielded values ranging from 3.4 to 6.5 mg. Such a fall could be due to the stress imposed by the operative procedure itself, and it need not necessarily be interpreted as being due to the removal of the tumor. Two months after the operation the excretion has risen to 8.5 mg. per twenty-four hours.

The urinary gonadotropic hormone output before operation was less than 4 mouse uterine units per day. This low value is of considerable interest when contrasted with a high level of 64 units obtained two months postoperatively. The latter high value is normal after the menopause, and the previous low excretion would be expected if there had been secretion of an active sex hormone by the tumor.

The preoperative excretion of estrogen was not high (less than 75 international units in twenty-four hours), and no pregnandiol was detected.

A high urinary output of 17-ketosteroids points rather definitely to adrenal origin of the tumor on the basis of previously reported cases. In the case reported here, on the basis of undeniable signs of masculinization and their regression following removal of the tumor, it seems permissible to assume that the preoperative level of 11.6 mg., though within the high limits of normal, represented a comparatively high level for this particular patient. The subsequent fluctuations post-operatively, varied between 3.4 and 8.5 mg. per twenty-four hours. This, in the light of the behavior of gonadotropic hormone, is of interest. Gonadotropic hormone varied between 4 Mu and 64, the postoperative level. This suggests a more or less typical castration reaction. In the light of the difficulty of identification of these tumors on the basis of lipoidal content or morphology, fluctuations in hormone output are all the more important in identification of these tumors.

### Summary

There are a number of features in this case that seem noteworthy, viz., although the patient gave a history of menopause at 37 years with rather

The figures therefore depend entirely on the size and shape of the individual, and, in order to obtain good end results, each patient must be calibrated.

The radium dose which assures a complete amenorrhea is about 1,800 mg. element hours. The method employed is to insert a 2 mm. brass capsule containing 50 mg. of radium into the uterine cavity for a period of thirty-five hours. The capsule should be placed at the fundus of the uterus to avoid subsequent scar tissue formation with stenosis of the cervix and a resultant pyometria. Diagnostic curettage and a microscopic examination of all scrapings precedes both types of therapy to exclude the existence of carcinoma, sarcoma or tuberculosis. This type of treatment should not be administered by the radiologist, but by the gynecologist who can evaluate co-existing infections, malignancies, or complicating diseases which would contraindicate this method of therapy. The predilection of our clinic for radium application rather than roentgen-ray therapy is due to the fact that further irradiation is never necessary when a total of 1,800 mg. hr. has been given. Table I summarizes the results of the radiation therapy.

TABLE I. RADIUM THERAPY, 296 CASES

DOSE IN MG. EL. HOURS	NUMBER OF PATIENTS	INADEQUATE DOSAGE	FURTHER RADIA- TION REQUIRED
1,800	259	--	0
1,500-1,700	10	10	0
1,000-1,400	13	13	3
Less than 1,000	14	14	10
Total	296	37	13

As the graph shows, 37 cases were considered to be inadequately treated, since they had not received the prescribed total dosage. However, in this inadequately treated group only 17 required subsequent irradiation for persistent bleeding. The indication for the termination of the radium treatment in this inappropriately treated group was an elevation of temperature 100.6° F. or more that did not respond to antipyretics within one hour's time. The morbidity arising during the radium application in the 37 cases was the only complication encountered, there were no deaths resulting from its usage.

Permanent menolysis instituted by the roentgen-ray method is illustrated in Table II.

TABLE II. ROENTGEN RAY, 116 CASES

DOSE IN R UNITS	NUMBER OF PATIENTS	REPETITION OF TREATMENT
500 r	88	2
400 r	28	6
Total	116	8

In both groups of patients, curettements were performed by our clinic in 378 cases, while 34 cases were accepted with negative microscopic reports from referring physicians. In the event that subsequent bleeding occurs, another curettement is performed and microscopic examination repeated, as the danger of carcinoma always lurks in such instances.

Analysis of this group of 378 cases showed that the hospitalization period required an average of 56.4 hours. Not only is the limitation of expenditure curtailed, but the safety of the procedure and the immediate usefulness of the patient on her dismissal would seem to be a basis that cannot be comparable with major procedures.

## RADIUM AND ROENTGEN THERAPY IN THE TREATMENT OF MENOPAUSAL UTERINE BLEEDING\*

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THE control of functional climacteric uterine hemorrhage presents a problem in which there is no uniform consensus of opinion. Undoubtedly, this confusion arises from the abundance of conservative therapeutic procedures available, or the radical surgical cures effective when conservatism fails. It is obvious that since the advent of radiation therapy, the impression has been created that such a method of treatment has displaced the medical and surgical procedures. In view of the multitude of methods proposed for benign uterine bleedings, it is apparent that each type of treatment has definite indications and limitations which should not overlap one another. It was considered of interest, therefore, to study a series of menopausal cases in which uterine hemorrhage was the indication for radiation therapy.

### Material Studied

The material is based on a survey of 412 consecutive records covering a five-year period from 1939 through 1943, inclusive. This has given us a range of two to seven years follow-up in which to formulate later conclusions. All patients from this group were subjected to a course of radium or roentgen-ray therapy, administered to control idiopathic bleeding. Of the 412 patients, 116 cases, or 28.05 per cent, received treatment with the roentgen ray, while in 296 women, or 71.8 per cent, the radium application was used. The predominance of radium-controlled patients in this group of cases is explained on the basis that

1. Subsequent treatment is rarely needed when this form of therapy is applied, and
2. Curettage always precedes it.

### Technique and Dosage

The roentgen dose for the production of a permanent menolysis is approximately 500 r into the midpelvis and attained through two fields, one suprapubic and one sacral. The kilo-voltage should be 200 and the filter 0.5 to 1 mm. of copper plus 1.0 mm. of aluminum. The output of the transformer and the Coolidge tube must be standardized with r meters to attain the expected results. The tissue dose is calculated as follows: The outline of the body surface is taken with calipers and drawn on tracing linen. The depth of the pelvis is then measured from the pattern produced by transverse and longitudinal sections from the points of widest separation. The estimated depth in centimeters is then compared with a standard absorption graph so that the maximum intensity and absorption are produced in the midpelvic region.

\*Presented before the Chicago Gynecological Society, March 15, 1946.

negative histologic examination associated with the menorrhagia establish the primary indication for radiation therapy.

The age variation for this five-year survey ranged from 40 to 51 years, with the maximal frequency established in the group from 44 to 47 years of age. The observation is made that the age distribution is of importance in that it parallels the carcinoma age curve.

Clinical Postirradiative Results

The early local effects of radiation therapy coinciding with the cessation of ovarian activity are the objections predominantly offered by clinicians. However, the cervical discharge produced for a period of six to eight weeks is comparable with the leucorrheas of cervical cauterizations or the granulation irritations of vaginal hysterectomies and plastic operations. Accentuation of the menopausal syndrome is not the troublesome complication as has been frequently emphasized. In our experience, the simplicity in which the uterine bleeding is controlled affords such relief to the patient that subsequent symptoms are minimized.

A survey of the clinical results, as presented in Table IV, may enable one to form a relative opinion on the therapeutic efficacy produced. These symptoms are presented in their order of frequency and are tabulated from the time of the treatment through the years of follow-up.

TABLE IV. CLINICAL EFFECTS OF RADIATION THERAPY

SYMPTOMS	CASES	PERCENTAGE
1. Menopausal manifestations		
A. Mild or no symptoms	214	51.90
B. Moderate	182	44.10
C. Severe	16	3.80
2. Leucorrhea		
A. Mild or none six to eight weeks postirradiative	316	76.60
B. Moderate eight to sixteen weeks	94	22.80
C. Prolonged twenty weeks or more	2	0.40
3. Cystitis (immediate—not prolonged)	28	6.70
4. Gastrointestinal	15	3.60
A. Nausea and vomiting	8	
B. Diarrhea	6	
C. Rectal bleeding	1	
5. Involutional melancholia	1	0.24

No attempt has been made to subdivide such symptoms by the mode of radiation therapy, since such disturbances do not greatly differ whether induced by radium or roentgen ray. The analyzed results are well within the limits of such investigators as Shriener, Norris, Behney, and others who have reached the same conclusions. Rongy, in his series, reports mild or no symptoms in 49.7 per cent of cases, moderate in 40.6 per cent, and severe in 3.7 per cent. It must be remembered that absolute hypo-ovarianism does not result from such therapy, and can never be compared with the complete ovarian deficiency in the bilateral oophorectomized women.

Complicating Pathology and Mortality

In this series, the number of myomas associated with benign uterine bleeding totaled 236 cases. These patients were in full accord with the indications

### Symptomatology and Age Incidence

The nature of the symptoms presented by the patient in no way formulates nor establishes a standardized form of treatment. The cardinal symptoms which impel these patients to seek medical advice are as follows:

1. Profuse or irregular vaginal bleeding.
2. Failure of previous conservative therapy.
3. Desire to avoid major surgical procedures.
4. Fear of a malignancy.
5. Co-existing pathology elsewhere in the body. Undoubtedly, the worries produced by the abnormal bleeding is not sufficient enough to impress upon these women the importance of a prompt medical investigation. Table III illustrates the relationship of the benign uterine bleeding and its duration to the previous investigation and previous management.

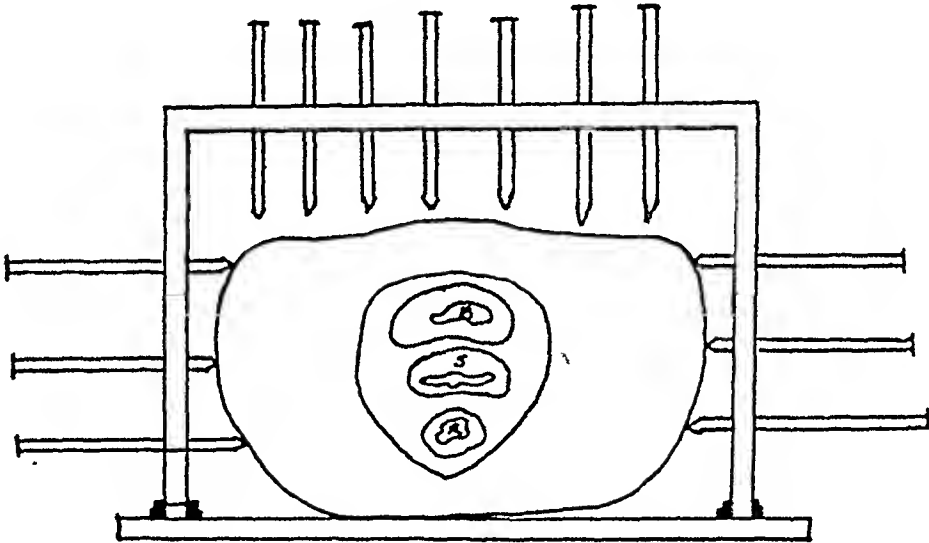


Fig. 1.—Redrawn from *Radiology*, Journal of the Radiological Society of North America 17: 1230, 1921.

TABLE III. DURATION OF MENORRHAGIA AND PREVIOUS TREATMENT

DURATION OF THE ABNORMAL BLEEDING	NO PREVIOUS TREATMENT	PREVIOUS ENDOCRINE THERAPY	PREVIOUS CURETTEMENT BUT NOT CURATIVE
1- 6 months	146	8	0
6-12 months	92	22	7
12-18 months	48	19	6
18-24 months	16	24	3
24-36 months	8	12	10
Total	310	85	26

Table III shows that 65 per cent of these women sought medical advice within the first twelve months. Such negligence occurring in a similar group of patients suffering from carcinoma would certainly postpone their chances of survival.

It must be emphasized that such patients suffering from uterine bleeding should not be irradiated until all underlying causes have been eliminated and a correct diagnosis established. The sequence of the onset of the menopausal syndrome, the age of the patient, essentially negative pelvic findings, and a

One should remember that acquainting the woman with the physiology of the induced climacteric is a keystone in this type of therapy. Manifestations of melancholia, psychic aberrations, or emotional instabilities should be carefully studied before suggestive therapy is undertaken. These are recognized states that became manifested at the climacteric, and not only are a menace for surgical procedures, but distinctly contraindicate radiation management. The psychologic attitude of both husband and wife should be considered in the treatment of these patients. Marital difficulties are often averted where an attempt has been made to conserve the pelvic organs rather than remove them. Radiation castration does not greatly influence the sexual congress of the couple, nor does it produce tissue changes which result in dyspareunia. Plastic operations performed in conjunction with radium or at a later date do not delay healing, nor do they prolong the period of convalescence.

A general attitude of pessimism is usually prevalent when radiation therapy for benign uterine hemorrhage is discussed. Yet when a careful clinical study predisposes the therapy, good end results are obtained that cannot be equalled by major surgical operations. In bleeding uteri due to benign causes, the method of treatment in well-selected, uncomplicated cases is radiation therapy.

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### Discussion

DR. JOHN I. BREWER.—The use of the terms "menopausal uterine bleeding" and "functional climacteric uterine hemorrhage" indicates that the patients reported had no pelvic pathology to account for the bleeding. However, this is not the case in this study, since over 50 per cent of the patients had uterine fibroids. The report as presented might well divide the patients into two groups, those with and those without pelvic pathology. As presented, the author deals simultaneously with irradiation therapy of bleeding in patients with and without fibroids. This is done in spite of the fact that the author states that "essentially negative pelvic findings . . . establish the primary indication for radiation therapy."

The relatively large number of patients treated with irradiation methods exceeds greatly the number so treated by our group. It is believed that, unless contraindicated, surgery offers the most suitable method of treatment. Curettage is recommended prior to irradiation, and we are in accord and wish to stress that it must be done. However, if a sarcoma is located in a fibroid and not in the endometrium, curettage will not establish the diagnosis, and the amount of irradiation used is not adequate treatment. That this circumstance is not too infrequent is borne out by the fact that two patients operated upon by our group in the past two months had just such sarcomas.

It is also believed that a patient 40 years of age who has fibroids and is bleeding is preferably treated with surgery rather than irradiation in order that ovarian function can



in that the myomas were no larger than a three months' gestation, located intramurally and occurring during the menopausal years. Only one case was later subjected to a subtotal hysterectomy for persistent pain attributed to a degeneration of the myoma. Table V illustrates the number of complicating lesions which were co-existent at the time of the radiation therapy. Uterine bleedings associated with such serious diseases were terminated by this method to minimize the risk of additional blood loss and to avoid major pelvic procedures.

TABLE V. COMPLICATING PATHOLOGY AND MORTALITY

PATHOLOGY	NUMBER OF CASES	RESULTS
Myomas—less than three months' gestation	236	1 supracervical hysterectomy
Cardiac Pathology		
Rheumatic heart Gr. IV	3	2 died within one year
Endocarditis	1	died in six months
Coronary heart disease	1	died suddenly 3 years
Myocarditis	1	uneventful
Active Tuberculosis	1	survived
Diabetes Mellitus	1	survived
Chronic Nephritis	1	survived
No Pathology	167	1 death second year, meningitis

All of the deaths in this group of cases were due to the co-existing pathologic lesions and comprised five cases, or an uncorrected mortality of 1.2 per cent. There were no deaths resulting from sepsis or as a direct result of the radiation therapy.

Previous pelvic surgery in no way contraindicates this type of management, but rather aids in obviating the dangers of additional surgery. The problem which presents itself is what course to pursue, and this depends entirely on the type of previous surgery. It is our custom in the presence of acutely ante flexed uteri from previous suspensions or interposition operations to advocate the roentgen ray management. Insertion of a radium capsule in an angulated uterus is a difficult procedure which would increase the hazards of its use. There were 56 patients encountered in this group that had previously received some type of pelvic surgery. The interval elapsing from the time of the surgical procedure until radiation therapy was instituted varied from twenty-two months to three years. The various types of operations and the method of treatment instituted are detailed in Table VI.

TABLE VI. PREVIOUS PELVIC SURGICAL PROCEDURES AND TYPE OF RADIATION THERAPY

TYPE OF PREVIOUS PELVIC SURGERY	NUMBER OF CASES	RADIATION METHOD	
		ROENTGEN RAY	RADIUM
Watkins' interposition	2	2	—
Myomectomies	6	1	5
Suspensions of uterus	17	15	2
Salpingectomies	15	2	13
Defundations	3	2	1
Manchester	1	—	1
Ovarian cystectomies	5	1	4
Amputations of cervix	2	—	2
Celporrhaphies	5	—	5
Total	56	22	32

at once. Three months later the uterus is removed. I have never encountered additional difficulties because of this procedure.

I think Corseaden's paper has to be interpreted a little differently. He comes to the conclusion that 9.6 per cent of these patients develop carcinoma. Clyde Randall, in his study, found a similar incidence of malignancy in women with bleeding problems approaching 40 years of age. I think that would have occurred whether the patient had radium or not.

Dr. Edwards, we did not do these previous operative procedures. We agree with you on condemning many of these operations, but the patients had had these operations before coming to us. We used radiation to correct the bleeding which had not been corrected by the previous procedure.

DR. TOWNE (Closing).—As to the occurrence of cystitis, that is due to poorly planned radiation. If you give 1800 mg. hr. in the uterus and pack the vagina well in order to keep the bladder and rectum away, cystitis, proctitis, faecal ulcer, or bowel injury should not occur. That is why we favor intrauterine radium, because we can protect the bladder and bowel. With x-ray, we cannot protect these structures as well.

be maintained. I cannot subscribe to the contention presented in this paper that women over 40 years of age are menopausal.

**DR. ARTHUR K. KOFF.**—There are four, more or less accepted, methods of treating benign uterine bleeding of the menopause: (1) endocrine; (2) curettage alone; (3) curettage followed by intrauterine radium or deep x-ray; (4) curettage followed by hysterectomy with or without removal of both ovaries.

I am of the opinion that endocrine therapy has no place in the treatment of benign uterine bleeding of the menopause, because the specialist treating women of this age group must make a complete diagnosis by curettage before instituting any form of therapy, and this cannot be accomplished as an office procedure.

Second, curettage alone is successful in curing approximately 20 per cent of these cases, and this procedure should be limited to those patients who insist on retaining some ovarian function.

Third, curettage followed by deep x-ray, or particularly intrauterine radium, as Dr. Towne has so clearly shown, is a safe and effective procedure and has the added advantages of a short stay in the hospital (two days or less), a minimum of disability to the patient and at the same time is more economic.

Curettage followed by hysterectomy, on the face of things, appears to be a radical procedure. Nevertheless, in view of the work of Corsecaden and his associates, we may regard hysterectomy as the procedure of choice in benign bleeding of the menopause. These authors point out that, on a statistical basis, 9.6 per cent of women 30 to 55 years of age requiring treatment for excessive uterine bleeding will, sooner or later, develop carcinoma of the uterus. In comparison to women of the same age group in the general population, the incidence of carcinoma of the uterus is approximately one-third as great. Moreover, there is an abnormal preponderance of carcinoma of the corpus in relation to that of the cervix—two to one, respectively. If more extended studies show that this very real danger is present, then a prophylactic complete hysterectomy may be the procedure of choice.

**DR. CHARLES E. GALLOWAY.**—There is one other point in Dr. Corsecaden's paper that I thought should have been brought out, and that is that women who have had radium or x-ray treatment for menopausal bleeding are three to four times as likely to go ahead and develop carcinoma of the fundus as those that were not treated; in other words, they have found that the incidence of carcinoma of the fundus which followed application of radium and x-ray is about four times that in women with menopausal bleeding who did not have x-ray and radium.

Another point that should be brought out is that a woman that has had radium and x-ray may come in five years later with a severe persistent cystitis. The effect of radium and x-ray is not fully appreciated. It causes endarteritis and lesions similar to lesions seen in syphilis, and it can even cause late anemic infarcts. The late effect of radium and x-ray may appear as long as four to six years after its use. I am not in favor of applying radium and x-ray for menopausal bleeding. If a woman is over 40 years old, I think the uterus should be taken out rather than be treated with radium and x-ray.

**DR. SCHMITZ (Closing).**—These were consecutive cases from our private service and, therefore, could be followed very carefully.

I can agree with Dr. Brewer as to the use of the term benign uterine bleeding or menopausal bleeding in these patients where 50 per cent had myoma. We should divide them into two distinct groups.

As to tissue examination, this was by frozen section followed by paraffin section when the pathologist could not give us a positive report. I do not feel that this in any way interferes with treatment. I curette all uteri harboring carcinoma and insert radium

uninterrupted procedure and an uneventful postoperative recovery. Rapid induction of anesthesia, which saves time between operations, is also appreciated by the operator. The anesthetist's primary object is the safety of the patient. Besides satisfying the surgeon and the safety of the patient, he must reassure the patient freedom from pain. The most difficult task to overcome is the mental reaction of pain. Fear of pain, fear of loss of consciousness, and the outcome of the surgical procedure all combined throw the responsibility on the anesthetist. Besides the acute pathology for which surgery is being performed, he is confronted with the general physical condition of the patient. The type of surgical procedure, technique, and skill of the surgeon are also factors to be considered in the risk and outcome of the patient. Postoperative complications resulting from surgery, together with the pharmacologic effects of the various agents, are further considerations in the causation of postoperative sequelae.

No one method of anesthesia satisfies all the demands for the ideal agent. What may supply all the necessary requisites for the surgeon may be detrimental to the patient. Progress in the art and science of anesthesiology has permitted the anesthetist to choose a method and agents most suitable to the individual patient. Although one agent may not be satisfactory, a combination may serve the desired aim.

Individual agents have certain drawbacks. Nitrous oxide and oxygen is a pleasant and safe anesthetic, but is inadequate for relaxation. The addition of ether overcomes this difficulty. While ether is safe, it has certain disadvantages. It causes gastrointestinal upset, metabolic disturbances, and irritation of the respiratory tract. It is also inflammable when administered with nitrous oxide and oxygen. Chloroform and ethyl chloride are cardiac depressants. Cyclopropane may also be toxic to the heart. Spinal anesthesia, although it gives excellent relaxation, has several deleterious side-effects. Local and regional anesthesia have proved very satisfactory, but they have their limitations, and often must be supplemented with some other form of anesthesia besides leaving certain impressions which make subsequent surgery fearful.

Intravenous anesthesia has many contraindications. The many drugs used have been condemned as dangerous and impractical. Many of the others, while safe, have an action that is too short to produce adequate surgical anesthesia. Barbiturates for the intravenous route are safe and satisfactory for short procedures and for those requiring only moderate surgical relaxation. However, intravenous method has many advantages, and has displaced other methods in many branches of surgery. Briefly, those advantages can be enumerated as follows:

1. Rapid induction—psychic shock is minimized.
2. Easy induction—the patient falls asleep and quietly passes into a stage of surgical anesthesia. No coughing—no excitement—no struggling—no tendency to vomit.
3. Injection is pleasant, and there is no fear of subsequent injections.
4. Dosage is easily controlled.

# SODIUM PENTOTHAL ANESTHESIA IN MAJOR OBSTETRIC AND GYNECOLOGIC SURGERY\*

## Preliminary Report of 300 Cases

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WITH the development of modern anesthesia into an art and science instead of a minor technical procedure of the medical curriculum, great progress has been made in the relief of pain and fear of surgery. The various agents and methods of administration used have been most dangerous, with resulting fatalities in the hands of the inexperienced. Within recent years, this infant science has made great progress since the organization of the American Board of Anesthesiology. Its founders, realizing the importance of this medical blessing as a necessity of life, have attempted and succeeded in continuing the many researches on this pain- and fear-relieving branch of medical science. Besides, they have set up the proper standards for its members, educated the profession as to the many important phases of this specialty, so that the public may profit and avail itself of the new agents without the empirical trial resulting fatalities of the inexperienced. Along with the development of this science came the use of intravenous anesthesia, which is one of the most impressive types of anesthesia of modern medicine. Pentothal sodium is the agent used when speaking of the intravenous method. This agent is a barbituric acid derivative, an American-made improvement on the older European evipal. The credit for introducing sodium pentothal into clinical surgery belongs mainly to Dr. John S. Lundy, whose work and researches at the Mayo Clinic can be considered great advances in modern anesthesiology.

Intravenous general anesthesia had its inception in 1872. During this period, it has had many setbacks because of the lack of suitable agents. This method of anesthesia has made great strides during the past decade. The many researches on the barbiturates, and the transformation of the administration of anesthetics into the art and science of anesthesiology have both played an important role in its development. Intravenous anesthesia has displaced other methods of anesthesia in many fields of surgery. Its future will depend on further researches in the development of new agents, and its use in combination with other methods.

At present, there is no one method of anesthesia that is ideal for every procedure from the point of view of the surgeon, anesthetist, and the patient. The surgeon is primarily interested in the safety of the patient, then he will consider relaxation and other factors which will permit him to carry out an

\*Read at a meeting of the New York Obstetrical Society, Feb. 12, 1946.

cesarean sections, 0.4 to 0.6 mg. of atropine sulfate was administered half an hour preoperatively. These patients received 5 e.e. of 2 per cent solution. The patient's reaction was then observed, and 2 or 3 c.c. injected repeatedly until the patient was ready for surgery. The initial dose varied from 10 to 20 e.e. of a 2 per cent solution.

For vaginal plasties, etc., the initial dose was smaller, from 8 e.e. to 15 e.e. of solution was required before the patient was ready for surgery.

The site of injection was median basilic vein or the veins of the hand, as per diagram.

Preliminary Medication

As routine, this series of cases received a dose of 7½ grains of veronal or some barbiturate derivative the night before operation. One hour prior to operation, a hypodermic injection of ⅙ grain (0.01 Gm.) of morphine sulfate and ⅓150 grain (0.00043 Gm.) of atropine sulfate was given. Since most of the barbiturates are respiratory depressants, an attempt was made not to give too many drugs which depress the respiratory center. Although the amount of drug required would be less if more barbiturates were administered preoperatively, still it was the author's wish to determine the value of intravenous anesthesia with sodium pentothal for general major surgery and compare its effectiveness with the modern agents used in our hospitals. For cesarean section ⅓150 grain (0.00043 Gm.) of atropine was given without morphine.

Data

Three hundred consecutive major obstetric and gynecologic cases were studied in which sodium pentothal was the anesthetic employed (Table I). There were 50 obstetric and 250 gynecologic cases.

*Obstetric.*—(Table II.) There were 45 cases of cesarean operations. In this group, the average amount of sodium pentothal used was 1.14 Gm. and the average anesthesia time was forty-five minutes. The smallest amount of agent was 0.4 Gm. and the largest was 1.6 Gm. The shortest anesthesia time was twenty-five minutes, and the longest was sixty minutes.

*Cesarean Section and Hysterectomy.*—Five cases. The average sodium pentothal used was 1.35 Gm., and the average anesthesia time was sixty-one minutes. The smallest amount was 1.2 Gm. and the largest 1.6 Gm. The shortest anesthesia time was sixty minutes, and the longest was sixty-five minutes.

*Gynecologic.*—(Tables III and IV.) The average amount of sodium pentothal used was a minimum of 0.89 Gm., the largest was 1.4 grams. The average shortest time was thirty-eight minutes, and the longest was seventy-one minutes. In this series, the smallest amount was 0.5 Gm., and the largest 2 grams. The shortest anesthetic time was twenty minutes, and the longest was one hundred twenty minutes.

TABLE I. SODIUM PENTOTHAL ANESTHESIA, 300 CASES

<i>Obstetric</i>		
Cesarean section	45	} Total 50
Cesarean section and supracervical hysterectomy	5	
<i>Gynecologic</i>		
Vaginal plasties	28	} Total 250
Vaginal plasties and vaginal hysterectomy	40	
Vaginal plasties and laparotomy for operations on uterus, tubes, and ovaries	40	
Vaginal hysterotomy	1	
Laparotomy for operations on uterus, tubes, and ovaries	47	
Supracervical hysterectomy	45	
Total hysterectomy	5	
Vaginal plasties and supracervical hysterectomy	44	

5. Recovery is rapid.
6. Absence of vomiting and distention.
7. Postoperative complications are few or none.
8. Blood pressure is maintained.
9. Ideal anesthetic for patients who fear induction of inhalation method.
10. Can be used as a supplemental agent.

The requisites for intravenous anesthesia are as follows:

1. Properly trained anesthetist.
2. Oxygen tank always available.
3. Airway tube available.
4. Proper technique for venepuncture.
5. Strict asepsis and antisepsis.
6. Freshly prepared solution of agent.
7. Pure, sterile, distilled water to be used to make solution.

### Pharmacology<sup>1</sup>

The prime features of the action of pentothal sodium consists of an effect which is produced promptly after the administration of the drug. It causes varying degrees of hypnosis, sedation, analgesia, anesthesia, and respiratory depression, depending on the size of the dose and its method of administration. The drug is a respiratory depressant and, except for its hypnotic action, depression is its foremost effect. The degree of depression is directly proportional to the size of the dose administered and the rapidity of intravenous injection.

Blood pressure falls temporarily and later is maintained. Rises in blood pressure have been reported. It causes a slight reduction in hemoglobin and erythrocytes in contrast to ether, which causes an increase. Blood sugar is not appreciably changed with pentothal anesthesia.

### Method of Administration

Many types of apparatus have been described in the literature for the administration of the intravenous method of anesthesia. In most of the cases of our series we have used a simple appliance as described by Dr. L. Pico,<sup>2</sup> Anesthetist at St. Peter's Hospital, Brooklyn, New York. For some of the cases the usual intravenous graduate gravity flask has been used. The object has been accomplished with the continuous infusion of a 2 per cent solution of sodium pentothal for induction, and a 1 per cent solution for a maintenance dose has been employed. With both systems, the rate of flow is controlled by the anesthetist, depending upon the desired plane of anesthesia to be reached. Each patient is an individual problem as to the amount and concentration of sodium pentothal required. The essential observation during the interval of induction is how the individual patient handles the anesthetic. It is during this phase that one determines when to dilute the solution from 2 per cent to 1 per cent, or even 0.5 per cent. The rate of infusion then depends on the depth of respiration, pulse, blood pressure, and, most important, the clinical picture of the patient.

Although each patient varies as to the dosage requirements, the following are the average dosages of 2 per cent sodium pentothal used for induction in our series.

Abdominal cases required 15 to 30 c.c. of 2 per cent solution before the proper stage was reached for the surgeon to start the operative procedure. In

TABLE VII. SODIUM PENTOTHAL ANESTHESIA

*Indications:*

1. Extremely nervous and apprehensive patients
2. Patients fearful of inhalation anesthesia
3. Patients intolerant to pain of local, region or spinal
4. Frail, debilitated patients in whom other methods are contraindicated

*Contraindications:*

1. Advanced cardiac disease with dyspnea
2. Toxemia
3. Obstruction of airways

largest was 2 Gm. The shortest anesthetic time was twenty minutes, and the longest was one hundred twenty minutes. There were no untoward maternal or fetal complications encountered (Tables V and VI). The infants did not show asphyxia, but seven of the series were drowsy and had to be stimulated. These occurred in the cases where the babies were not delivered within the five-minute period after incision was made. There were no maternal or fetal deaths. There was no unusual degree of postoperative bleeding noticed. The postoperative sequellae were excellent in the entire group of cases. Postoperative vomiting and distention were not present. Amnesia of events was marked, and the patients reacted as if they came out of a natural sleep. Pulmonary, circulatory, metabolic complications, and undue morbidity were not encountered. Patients had desire for food immediately after operation. The blood pressure was maintained. Peripheral circulation was good, the skin was blanched and warm. The majority of patients requested to urinate immediately after awakening.

Laryngeal spasm was observed in a few cases. This symptom is treated by adjusting the airway and slowly deepening the anesthesia. Tremors were not observed. Coughing and hiccoughs occurred temporarily, but disappeared after anesthesia became deeper.

Table VII gives outlines and indications and contraindications of intravenous sodium pentothal anesthesia.

### Summary

1. A series of 300 consecutive major obstetric and gynecologic cases using intravenous sodium pentothal anesthesia is reported.

2. The continuous method of intravenous administration of sodium pentothal is advocated using 2 per cent, 1 per cent, and 0.5 per cent solutions.

3. A dose of less than 1.5 Gm. of sodium pentothal was used by this method in this series.

4. No maternal or fetal deaths, or no postoperative complications were encountered.

5. The indications, contra-indications, requisites, advantages and disadvantages have been discussed.

### Conclusions

1. Sodium pentothal intravenous general anesthesia can be used with success in major obstetric and gynecologic surgery.

2. It is a safe anesthetic for the patients, for its dangers are minimal in the hands of a competent properly trained anesthetist. In cesarean section,



TABLE II. AMOUNT SODIUM PENTOTHAL AND TIME OF ANESTHESIA

OPERATION	NUMBER OF CASES	AVERAGE AMOUNT OF DRUG (GM.)	AVERAGE TIME OF ANESTHESIA (MINUTES)
<i>Obstetrical</i>			
Cesarean	45	1.14	45
Cesarean and hysterectomy	5	1.35	61

TABLE III. AMOUNT SODIUM PENTOTHAL AND TIME OF ANESTHESIA

OPERATION	NUMBER OF CASES	AVERAGE AMOUNT OF DRUG (GM.)	AVERAGE TIME OF ANESTHESIA (MINUTES)
<i>Gynecologic</i>			
Vaginal plasties	28	0.89	38
Vaginal plasties and vaginal hysterectomy	40	1.17	54
Vaginal plasties and laparotomy	40	1.35	63
Vaginal hysterotomy	1	1.10	40
Laparotomy, operation on uterus, tubes, ovaries	47	1.40	52
Supracervical hysterectomy	45	1.28	58
Total hysterectomy	5	1.20	70
Vaginal plasties and supracervical hysterectomy	44	1.40	71

TABLE IV. DOSAGE AND ANESTHESIA TIME

<i>Dose</i>	
Minimum	0.89 Gm.
Largest	1.40 Gm.
<i>Time</i>	
Shortest	38 minutes
Longest	71 minutes

TABLE V. OBSTETRIC SEQUELLAE

Maternal and fetal deaths	0
Asphyxia	1
Drowsy	7
Postoperative bleeding	0
Postoperative shock	0

TABLE VI. GYNECOLOGIC SEQUELLAE

Maternal deaths	} None
Complications, pulmonary, circulatory	
Vomiting and distention	
Shock	
Fear	
Tremor	} All
Rapid recovery	
Desire to sleep	
Desire to void	
Amnesia	} Few
Laryngeal spasm	
Coughing and hiccoughs (?)	

Analysis of Data

In this series of 300 major obstetric and gynecologic cases, the smallest amount of agent used was 0.4 Gm., and the largest was 1.6 Gm. in the obstetric cases. In the gynecologic cases, the smallest amount was 0.5 Gm. and the

## LEUCOPLAKIA VULVAE

### Its Etiology and Results of Treatment With Vitamin A

#### Preliminary Report

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FOR the past four years the authors have studied the many perplexing aspects of leucoplakia vulvae and its relations to kraurosis, atrophic dermatitis, and vulvar carcinoma. This preliminary report will be limited to the discussion of its etiology and to our experience in its treatment with vitamin A.

Our investigation comprises a group of 18 patients, in all of whom the diagnosis has been verified by histologic examinations. Each patient was subjected to a thorough complete physical examination and checked by carefully supervised laboratory tests. The routine followed was as given below:

1. Complete blood count.
2. Blood chemistry for glucose, urea nitrogen, nonprotein nitrogen, cholesterol, whole blood chlorides, CO<sub>2</sub> combining power, icterus index, and calcium.
3. Vitamin assays of A and C. Rate of absorption and excretion of B<sub>6</sub>.
4. Basal metabolism.
5. Blood Wassermann and Kahn tests.
6. Urinalysis.
7. Determination of estrogenic and gonadotropic hormone content of the urine.
8. Analysis of gastric contents for free HCl and total acidity after an Ewald meal.

With the exception of the gastric contents examination, which in approximately 60 per cent of our cases showed little or no free hydrochloric acid, all our other tests were substantially negative from the diagnostic standpoint. Compared to the normal physiologic incidence of anacidity of 35 per cent for any similar age group, our figure is definitely abnormally high. This important observation, originally made by Swift<sup>1</sup> of Australia, is the first intimation of record regarding the possibility of its being of etiologic significance in the pathogenesis of leucoplakia vulvae.

Clinical studies in other fields have demonstrated the relationship existing between gastric anacidity and the low plasma level of vitamin A. Premature infants have little or no free hydrochloric acid in the stomach with a concomitant low plasma level of vitamin A: nutritional improvement takes place after the administration of lactic acid milk and a proved rise in the plasma level of vitamin A. Similarly, in certain diseases of adult life, as in carcinoma of the stomach and in pernicious anemia, the plasma level of vitamin A is either low or entirely absent. In both these conditions there is either complete anacidity or subacidity of the gastric contents. However, in the presence of

precaution should be taken that the baby is delivered within five minutes from injection.

3. It is an excellent anesthetic for debilitated and aged patients in whom other forms of anesthesia are contraindicated.

4. Sodium pentothal does not give good relaxation for extensive abdominal procedures, but it can be supplemented by other methods. Further researches may overcome this difficulty.

I would like to acknowledge my thanks to Dr. L. Pico of the Department of Anesthesia at St. Peters Hospital, and to the Staff of the School of Nursing of the Long Island College Hospital for the cooperation and observations of the cases studied. I am indebted to Dr. L. Pico for his enthusiasm, cooperation, and administration of anesthesia in most of these cases.

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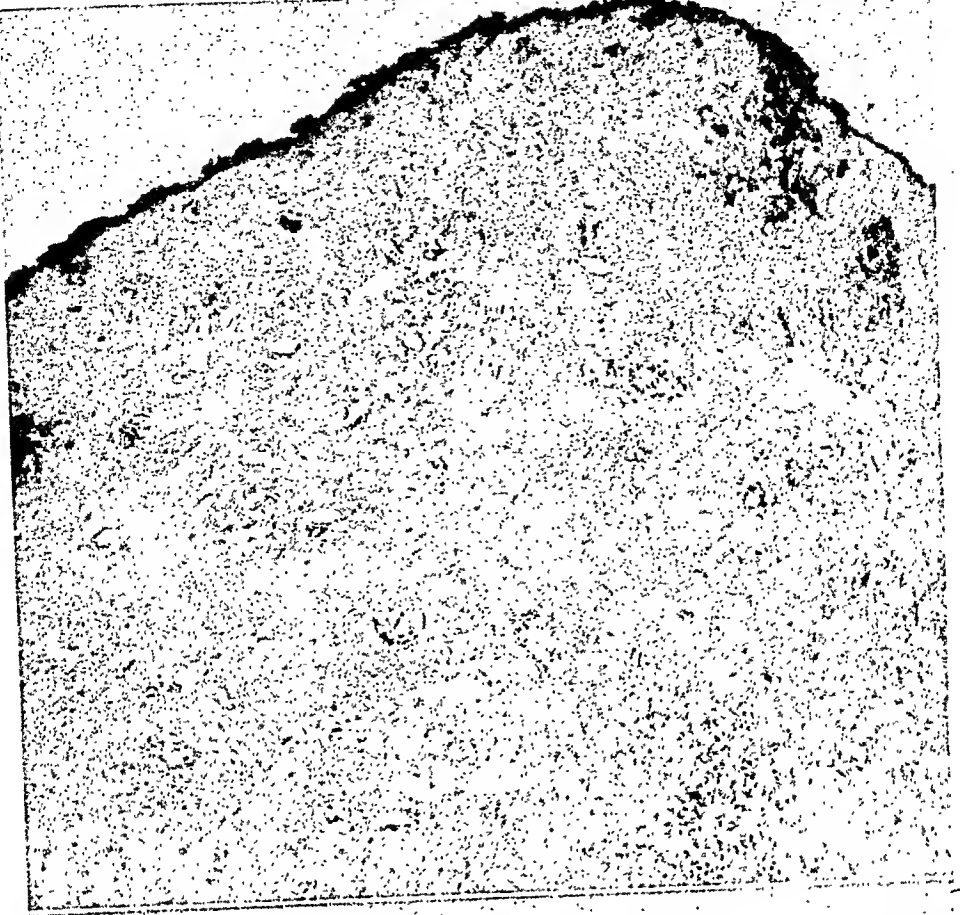


Fig. 3.

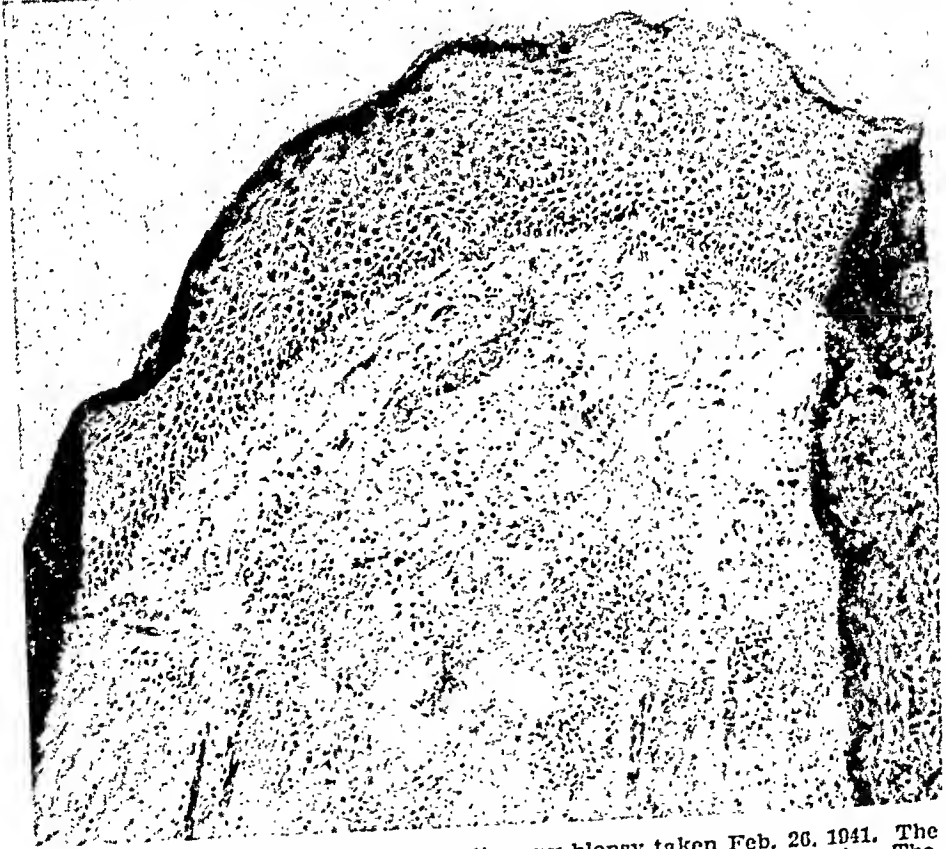


Fig. 4.

Fig. 3.—A. DeR., Chart No. J 72544. Pretherapy biopsy taken Feb. 26, 1941. The epidermis seems mildly acanthotic with some degree of hyperplasia and hyperkeratosis. The dermis is fairly compact with a mildly intense infiltration by chronic inflammatory cells.

Fig. 4.—A. DeR. Posttherapy biopsy taken Oct. 28, 1942. There is a rather thin epidermis without rete pegs, and a loose vascular stroma irregularly and slightly infiltrated by a few chronic inflammatory cells. The histologic picture of the previous biopsy appears to represent a markedly more severe involvement than that of the present biopsy. "If these specimens are taken from quite comparable areas, there has been a striking change indeed." (Quoted from biopsy report.)

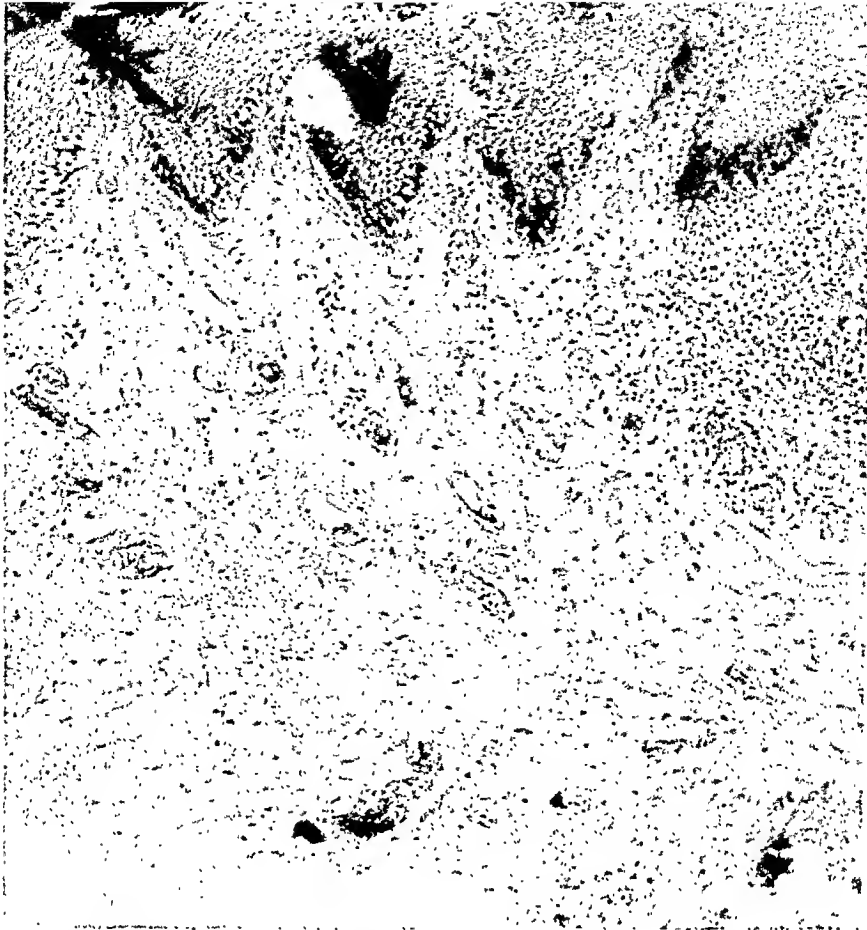


Fig. 1.

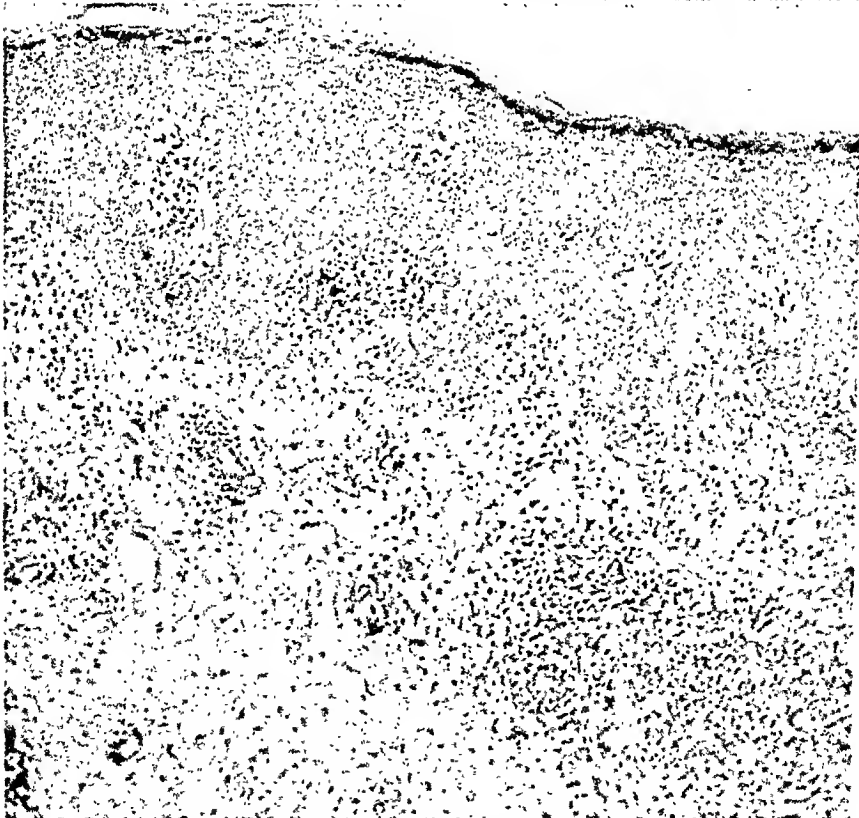


Fig. 2.

Fig. 1.—M. S. Chart No. 16927 D. Pretherapy biopsy taken July 21, 1941. The epidermis shows a mild acanthosis, the increase in thickness affecting principally the rete pegs which are slightly elongated, slightly widened and bulbous and which vary moderately in size and shape. The overgrowth involves all layers, the granulosa cell layer being several cells thick and the surface is covered by a slightly thickened horny layer. The dermis is finely fibrillar, loose in structure, suggesting edema, presents a few small, dilated blood vessels and focal collections principally in the papillary bodies of chronic inflammatory cells, chiefly lymphocytes and a few plasma cells and other mononuclear cells.

Fig. 2.—M. S. Posttherapy biopsy taken March 11, 1943. This specimen shows a thinner epidermis than in the first specimen, although there are still focal areas of epidermal thickening: the stratum corneum, however, is thin. The dermis, unlike the first specimen, is more compact, does not show the edema, but the amount of inflammatory infiltration is about the same.

the *normal* plasma levels of vitamin A in our cases, we can consider leucoplakia vulvae as being due to a subclinical deficiency of this vitamin. We are now checking our cases for vitamin A tolerance, similar to sugar tolerance tests in diabetic patients. It may be possible by this test to be able to determine the factors necessary to correlate the part played by vitamin A and gastric acidity in the pathogenesis of leucoplakia vulvae. The evaluation of these factors and their etiological importance will be discussed in a subsequent paper.

Proper treatment of disease is predicated upon its etiology, primarily. For the past decade, leucoplakia was considered due to an estrin deficiency. This concept had, and still has, many supporters. The numerous substantiating reports are evidence of the prevalence of this concept. In our experience, estrin administered in adequate dosage either by inunction, injection, orally, or by suppository, not only failed to relieve the local condition, but apparently produced, or rather was followed by, an aggravation of the symptoms in all our cases. Therefore, we cannot accept the cause of leucoplakia vulvae to be estrin deficiency.

In 1891, Bessnier suggested the term "leucokeratosis" for this condition. This is more correct histologically than "leucoplakia," originally advocated by Schwimmer<sup>2</sup> in 1877. The characteristic changes found on microscopic examination are hyperkeratosis, varying degrees of acanthosis, and hypertrophy of the rete Malpighii. The hyperkeratosis and acanthosis seemed a logical indication for the use of vitamin A therapy, as the role of this vitamin in ectodermal physiology is well known.

Wolbach and Howe<sup>3</sup> have demonstrated that in continued absence of vitamin A from the diet, the most prominent changes following this deficiency are a transition in which the normal epithelium in various parts of the body is replaced by keratinized epithelium. In 1922 Evans and Bishop<sup>4</sup> found a persisting cornification of epithelial cells present in the vaginal smears of rats, which had been oophorectomized previously, during a diet test in which vitamin A was pathologically deficient or entirely absent. Relief and even cure of keratosis follicularis (Darier's), ichthyosis, and other types of keratotic skin conditions are frequently reported in the literature. These may serve to indicate the basis for the treatment of leucoplakia vulvae with vitamin A.

### Results

Of the 18 patients treated, 14 have been relieved both subjectively and objectively. The four unimproved cases suffered from some constitutional disease. Two were diabetic, one syphilitic, and one had a cardio-renal-vascular lesion. In our opinion, the presence of these complications interfered in some way with the proper assimilation and utilization of vitamin A. This gives additional support to our theory of the metabolic etiology of leucoplakia vulvae.

### Method

In all our patients vitamin A treatment was begun immediately after the complete examination, supplemented by histologic proof. The daily oral dosage varied from 250,000 units to 500,000 units, supplemented by injections of 50,000 units, twice weekly. In addition, each patient received 15 minims of dilute hydrochloric acid (U.S.P.) in water three times daily, with each meal. The immediate response to this form of therapy varied. In some the subjective



Fig. 5.

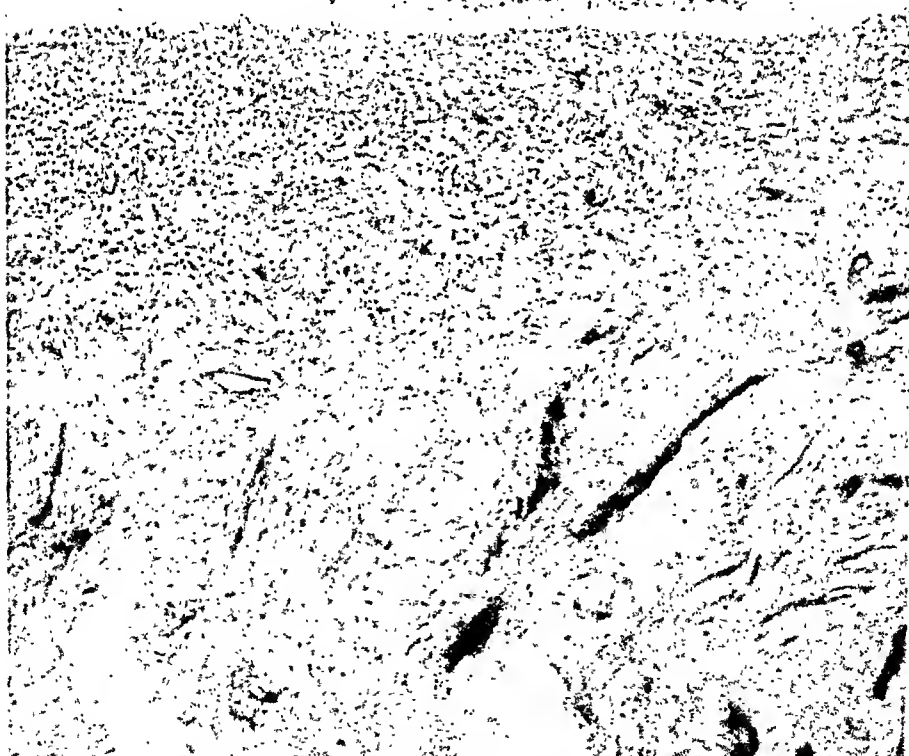


Fig. 6.

Fig. 5.—M. R., Chart No. 53187. Pretherapy biopsy taken Jan. 8, 1942. The epidermis shows variation in thickness. In some areas it is thin, with few or no rete pegs, while in others there is a distinct but slight acanthosis principally in the form of slightly elongated thick and thin pegs. There is focal hyperplasia of the granulo-cell layer, and the surface is covered by a generally slightly increased and variable thick layer of keratin. The dermis shows a fairly intense inflammation, particularly the papillary dermis, the infiltrating cells being irregularly scattered, some polymorphonuclear leucocytes, others mononuclears of various types. There is also a distinct dilatation and hyperemia of the small calibrated blood vessels.

Fig. 6.—M. R. Posttherapy biopsy taken March 11, 1942. In this specimen the epidermis is thin and without rete pegs, the granulo-cell layer represented at most by one or two cells, and keratin layer perhaps slightly thicker than to be expected. The dermis again shows inflammatory changes, but these are much less severe than in the first specimen.

4. Comparative microphotographs, pre- and posttherapy, show the improvement in and tendency toward the normal histologic architecture, in treated cases.

It is hoped that this report will stimulate further observation and therapy of this condition throughout the country, with the therapy outlined.

The authors express their gratitude and appreciation to Dr. Maurice Bruger, of the Physiologic Chemistry Department, for his wholehearted cooperation, and supervision of the laboratory studies.

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symptoms were relieved within several weeks; in others it was necessary to increase the amount of vitamin A, both orally and by injection, before any relief was manifested. No other form of local or constitutional therapy was given. Objective improvement seemed to run parallel to the degree of freedom from symptoms. The previously dry, indurated, glossy, and wrinkled external genitals became moist; the folds became fuller and the indurated skin again became pliable. However, our sole important index of improvement was the report of the histologic examination. Repeated biopsies revealed marked alteration in the degree of acanthosis and keratinization.

### Discussion

At present we have under observation six patients with a complete reversal of the pathohistologic findings, toward an apparently normal state. These patients have been without any type of treatment for at least two years, with no recurrence of symptoms. The remaining twelve are still under treatment. Biopsies from these patients show a definite improvement with a tendency toward normal histological structure of the skin. It is noteworthy that during this investigation period which has extended over four years no case in this series showed a tendency toward malignancy.

All biopsies, pre- and posttherapy, were taken from the most seemingly involved areas and not necessarily from comparable areas. The accompanying microphotographs of pre- and posttreatment biopsies of three cases offer an interesting exhibit of the results attained with our therapy.

All pretherapy specimens show a thickening of the epidermis, acanthosis, hyperkeratosis, an overgrowth of all layers. The dermis presents a picture of inflammatory reaction with an invasion of polymorphonuclear leucocytes, lymphocytes, and plasma cells. In most of our cases the diagnosis was minimal leucoplakia and the degree of involvement not severe.

The posttherapy biopsies reveal thinning of the epidermis, the keratin layer is thinner, the degree of acanthosis is less, and in two cases the hypertrophy of the rete pegs has disappeared. The dermal layer, still the seat of inflammation, shows a decrease in its intensity. It may be said that these represent a marked histologic improvement toward the normal.

### Conclusions

Based on our clinical study, herewith reported, we have reached the following conclusions:

1. Leucoplakia vulvae is of metabolic origin, due to a failure in utilization and/or absorption of vitamin A.
2. Uncomplicated cases of minimal leucoplakia can be relieved with adequate doses of vitamin A and dilute hydrochloric acid.
3. In four years of observation, not one case showed a tendency toward vulvar carcinoma. For this reason, we do not think that leucoplakia is a neoplastic disease.

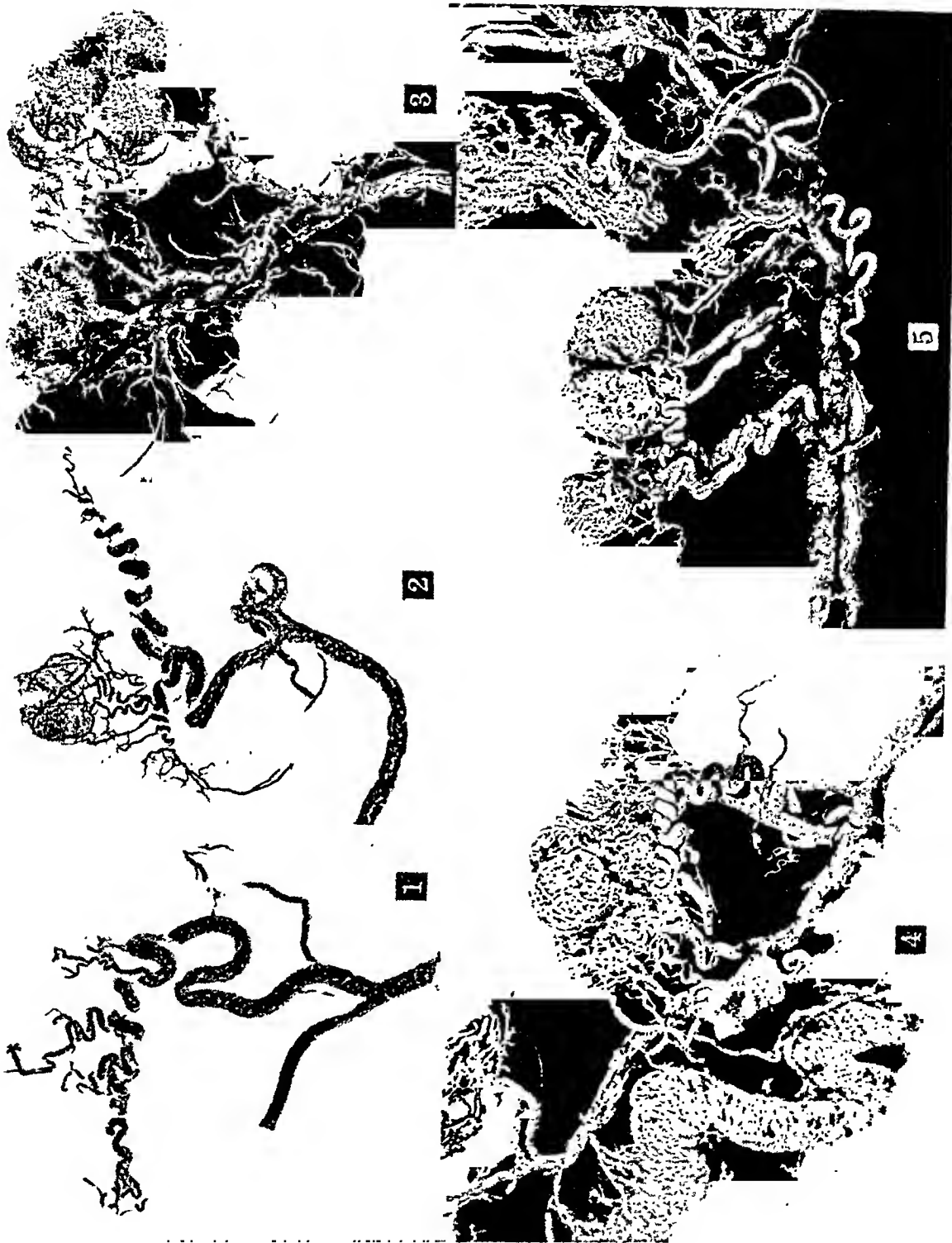


Plate I. Figs. 1 to 5.

Plates I and II.—Photographs of injection-corrosion of the blood vessels of the ovary of the rabbit, showing the spiral artery in the hilus of the ovary.

## Plate I.

Fig. 1.—Left ovary, twentieth day of pregnancy. Arteries only are injected, showing the ovarian artery, the ramus of the spiral, ending in a special artery which was contained in the hilus of the ovary. Terminal branches arise from the coils of the spiral. No corpora lutea were present in this ovary. (X3.)

## A SPIRAL ARTERY IN THE OVARY OF THE RABBIT

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A SPIRAL artery has been discovered in the hilus of the ovary of the rabbit. This was noticed during a study of the changes taking place in arrangement of the blood vessels in the wall of the uterus as this organ accommodates the products of conception. A series of injection-corrosion preparations of the rabbit uterus has been made. Along with injection of the blood vessels to and within the uterus, injection of the ovarian vessels was obtained. This note is written in order to describe the characteristic arterial pattern that is localized in the hilus of each of the ovaries obtained. Previous descriptions of the vascular pattern in the ovary, using other techniques, describe many important changes, but fail to note the existence of this spiral arrangement in the terminal portion of the ovarian artery.<sup>1-2</sup>

The ovarian artery makes a right angle turn cephalad as it enters the hilus, where it forms a helix of diminishing diameter extending throughout the length of the hilus. The arterial circulation to the rest of the ovary is derived from secondary or terminal branches from this artery. A second, very small spiral artery may arise at the base of the main spiral artery. It runs to the caudal pole of the ovary. There is no counterpart of this structure in the venous network within or from the ovary. The main arterial branch from the helix in the hilus of one ovary taken on the twelfth day of pregnancy (duration of pregnancy in the rabbit, thirty-two days) to an active corpus luteum was seen to be a spiral vessel also, but other, similar vessels have been seen which were merely buckled, tortuous structures. The characteristics of these vessels are shown in the accompanying photographs. For comparison, the venous network of the ovary is also presented. Dr. G. W. Corner and Dr. Elizabeth M. Ramsey have shown me a single rhesus monkey ovary, prepared after these rabbit ovary preparations were obtained, with an exactly similar spiral artery.

The method of demonstrating this was as follows: the aorta and inferior vena cava of an anesthetized rabbit were exposed and dissected free, caudal to the renal vessels. The femoral vessels were tied off, as well as any larger mesenteric blood vessels below the point of dissection. In some instances physiologic saline was washed through the blood vessels of the uterus and other organs and structures between the two points of ligature. In other instances, the injection-mass was injected directly, first into the artery, then into the vein. In some cases the veins only were injected, in others, the arteries only. The injection-masses were red (for arteries) and blue (for veins) vinylacetate in a 5 per cent solution of acetone.\* The injections were made into the aorta or the

\*This is available, ready for injection, from Ward's Natural Science Establishment, Rochester, N. Y.

inferior vena cava by syringe through an 18 or 20 gauge hypodermic needle about which a ligature had been tied. The tissues were allowed to remain in situ for about fifteen minutes, after which they were excised and put in corrosion fluid. This was about 2 per cent HCl to which about 1 teaspoonful of pepsin was added for each 500 c.c. of acid. The corrosion was allowed to proceed at 37° to 40° C. for twenty-four to forty-eight hours, or until all debris could be washed from the vinylite plastic under a small jet of water.

The significance of this spiral artery in the hilus of the ovary is, of course, speculative. Three implications suggest themselves to the writer, although the correctness of these should be established by further studies.

The first implication relates to the adaptation of the arterial circulation of the ovary to change in size of the ovary with age and reproductive state. In the rabbit, pregnant for the first time on attainment of maturity, the ovary is short and thin. It may contain a half-dozen or more corpora lutea. After many pregnancies, the ovary is increased considerably in length. The spiral arrangement of the main artery in the hilus of the ovary should permit a "paying out" of the coils of the helix as the growth of the ovary requires. If only a tortuous mass of arterial loops were present, it is conceivable that occlusion, to a certain degree, of the artery could occur.

The second implication relates to the hemodynamic aspect of the ovarian circulation. The condition to be fulfilled is one in which marked reduction of blood pressure occurs within the limited geometric and vascular space available. A moderately high arterial blood pressure necessarily diminishes to a level of the order of the partial osmotic pressure of the blood, for purposes of normal capillary exchange. A spiral arrangement of the type demonstrated should permit an orderly reduction in accordance with known hemodynamic mechanisms. In larger blood vessels, blood is moving at high velocity with correspondingly high kinetic energy along the axis of the blood vessel. With *reduction in size of vessel, with increase in length of vessel, or with change in direction of flow*, the velocity of the blood diminishes the kinetic energy diminishes accordingly. Concomitantly, potential energy (lateral pressure against the wall of the vessel) increases.<sup>3</sup> In a spiral artery of the type shown here, this would be accomplished in an orderly and progressive fashion, presumably with resulting equalization of the pressures within the branches from the spiral vessel to the structures within the ovary. If the artery were merely tortuous, it is unlikely that an equalized reduction of pressure within the arteries would occur throughout the ovary.

The third implication follows from the first two. It is that if the ovarian spiral artery serves (a) to allow normal adaptation to change in size of the ovary, and (b) to provide a mechanism for reducing and equalizing blood pressure throughout the ovarian stroma, then dysfunction, by altered morphologic relationships, or through the inroads of localized vascular degenerative or other types of diseases, may be related to certain types of ovarian pathology whose etiology is now obscure. Thus, there could be transmission of excessive pressure (i.e., above osmotic levels) which could contribute to development of cysts,

Fig. 2.—Right ovary, twentieth day of pregnancy. Arteries only injected, except that the injection mass was forced into the veins draining the corpus luteum through the vascular bed of this gland. The right vein has been blocked off in the negative. One corpus luteum is supplied by three terminal branches arising from a single artery arising from the caudal (left) spiral artery. This was in the hilus of this ovary. Small arterial branches to the fimbriae were cut off. (X3.)

Fig. 3.—Ovary with six corpora lutea on the sixteenth day of pregnancy. Injection of veins only. There is no spiral arrangement in the venous drainage system. (X3.) (Stereoscopic views at X3 and X12 show the intimate arrangement of these vessels in beautiful three-dimensional detail.)

Fig. 4.—Left ovary, twelfth day of pregnancy. Both arteries and veins were injected in red and blue. The spiral artery supplying four corpora lutea may be seen. The structures partly visible at the far left and right of this and Fig. 5, respectively, are the injected blood vessels of the ampullae and fimbriae of the Fallopian tubes. (X3.)

Fig. 5.—Right ovary, twelfth day of pregnancy. Three corpora lutea are present. Both arteries and veins were injected. The spiral artery may be seen in the position of the hilus of the ovary. The two vertical blood vessels passing behind the spiral artery are venous channels draining the corpora lutea. (X3.)

# PLATE II.

Fig. 6.—Detail of spiral artery shown in Fig. 2. See legend for Fig. 2 regarding the blocked-off portion of the vein from the corpus luteum. This picture is published for stereoscopic viewing which reveals the intimate details and relations of these vessels. It may be held in position in front of a hand-held, or other, stereoscopic viewer. (X8.)

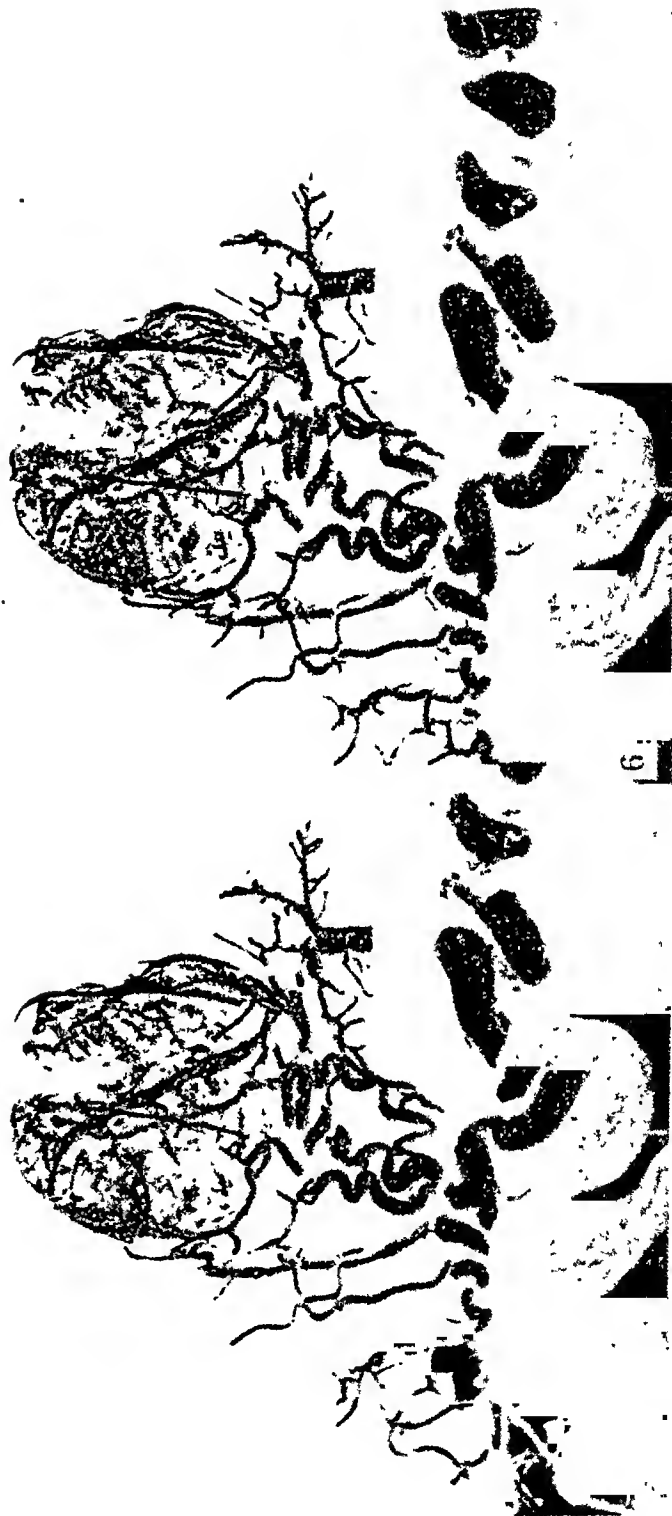


Plate II. Fig. 6.

## AN EVALUATION OF PRESACRAL NEURECTOMY IN THE TREATMENT OF DYSMENORRHEA

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THE first operative removal of the superior hypogastric plexus, or presacral nerve, as it is often called, for the relief of pelvic pain at the time of menstruation was performed at the Free Hospital for Women in 1931. Since that time our experience with the procedure has increased until by December, 1945, the operation had been performed 420 times, including the private cases of the staff. With this large experience came some fairly definite ideas as to the efficacy of the procedure and further notions as to its applicability. The purpose of this paper is to crystallize these impressions in some practical statistical way in order to confirm or to deny the generally accepted impressions of the value of the procedure itself. It should be stated that in most cases the operation was routinely combined with a dilatation and curettage, a suspension, and any other necessary pelvic surgery which the gynecologic situation demanded.

For a thorough description of the anatomy and physiology of the superior hypogastric plexus, one may refer to the papers by Pemberton<sup>1</sup> (1935) and Meigs<sup>2</sup> (1939). The recent paper by Waters<sup>3</sup> (1946) discusses more fully the rationale of the operation in the light of observations in spinal and caudal anesthesia. Rutherford<sup>4</sup> (1942) reviews the background and general literature regarding the operation in addition to presentation of cases. A general discussion of the basic etiology in essential dysmenorrhea appears in a paper by Fremont-Smith<sup>5</sup> (1942) with comments on medical management. Finally, in a paper soon to be published, Duncan,<sup>6</sup> of this clinic, describes in careful detail the steps of presacral neurectomy as it is now performed here, together with a discussion of proper application of the procedure itself. Cotte<sup>7</sup> (1937), in France, for whom the operation is sometimes named, reviews his large experience with the procedure, running to something over 300 neurectomies by 1937.

In order to assay the problem as accurately as possible, only the records of the ward patients at the Free Hospital for Women have been utilized, because they are more rigidly standardized as to form of history taking, operative description, and follow-up care. There were 255 such cases in the 15-year period to be covered in this report. The youngest patient was 14 years of age, and was submitted to neurectomy following the failure of medical treatment because she had been consistently unable to carry on with her schoolwork since menarche four years previously. The oldest patient was 40 years of age. The average age of patients, who constituted the essential dysmenorrhea group, was 24½ years, indicating, we feel, that we have not been unduly enthusiastic in too early an application of the operation. Thirty-nine per cent of these patients were married. The average age in the acquired group was 29 years, and 83 per cent of these patients were married.

or there could be excessive reduction of pressure and flow, transiently or persistently, in ways calculated to impair growth or development of tissues within the ovary.

There is no reason to suspect that this spiral artery of the ovary participates climactically in any normal ovarian functions in a manner comparable to the spiral arteries found in the basalis of the endometrium. But caution requires that this be borne in mind as a possibility in studies of cyclic phenomena in the ovary.

### Summary

A spiral artery within the hilus of the ovary is demonstrated. It is formed by a helix-type of formation from the ovarian artery as it enters the hilus of the ovary and turns sharply cephalad. Further vascularization of the ovary is accomplished by secondary branches arising from the coils of the spiral artery.

The speculative implications of this arrangement of the ovarian circulation are discussed in relation to (a) cyclic or periodic ovarian growth; (b) hemodynamic conditions within the uterus; and (c) to the etiology of ovarian pathology.

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1. Inadequate follow-up—eight cases. It was required as a routine of the clinic that the patient be seen at a six-week, a six-month, and a one-year visit, postoperatively. Cases seen only once are not included in this report.

2. Presacral neurectomy combined with hysterectomy—six cases. These were cases, in the early years, who had sufficient trouble in the pelvis to warrant hysterectomy at the time of initial laparotomy. It was soon discovered that their postoperative course was not materially altered or benefited, as compared with the patients having total hysterectomy alone, and the combined procedure was dropped. Obviously they are excluded from this report.

3. Presacral neurectomy performed for the relief of pain in advanced carcinoma of the cervix—three cases. Despite reports in the literature, not one of three such patients obtained any relief.

4. Diagnosis of dysmenorrhea not clear—1 case. That presacral neurectomy was performed in this case probably indicates that dysmenorrhea was present, but there was insufficient information to place the patient in either the acquired or the essential group.

5. Presacral neurectomy followed by x-ray sterilization for menorrhagia—1 case. With no further menstruation, the case was unsuitable for follow-up.

6. Major psychosis—1 case. This patient developed confirmed schizophrenia some time after the operation and became unsuitable for this study.

With these exceptions, then, there remain in the first 10-year period 116 cases for consideration. Of these, 78 cases, or 67.2 per cent, fall into the essential group and 38 cases, 32.8 per cent, fall into the acquired group.

TABLE I. PRESACRAL NEURECTOMIES—1931-1940, INCLUSIVE

<i>Total number of cases:</i> 136			
<i>Number of cases rejected:</i> 20			
1. Inadequate follow-up			8
2. Presacral neurectomy combined with hysterectomy			6
3. Advanced carcinoma of the cervix			3
4. Diagnosis of dysmenorrhea inconclusive			1
5. X-ray sterilization after neurectomy			1
6. Major psychosis			1
<i>Number of cases remaining:</i> 116			
<i>Essential Dysmenorrhea</i>		<i>Acquired Dysmenorrhea</i>	
78 cases—67.2%		38 cases—32.8%	
Complete relief	57—73%	Complete relief	14—37%
Partial relief	11—14%	Partial relief	10—26%
Total failure	10—13%	Total failure	14—37%

Complete relief was obtained in 57 cases of the essential dysmenorrhea group (73 per cent). Partial relief resulted in 11 (14 per cent) and total failure supervened in 10 (13 per cent). No further information during follow-up periods developed to explain these failures, but in a condition where the cause is admittedly so poorly understood, this is not surprising.

In the acquired dysmenorrhea group, however, the results are in striking contrast. Only 14 cases (37 per cent) were well following operation; 10 cases (26 per cent) were somewhat relieved; 14 cases (37 per cent) were not benefited in the least. Thus the total failures equaled the successes!

We turn now to a consideration of results in the recent five-year period. These are summarized in Table II. The follow-up here is shorter, of course, varying from two months to four years, and averaging twelve months. The total number of cases in this period was 119, of which 26 were rejected as follows.

1. Patients with essential dysmenorrhea and only one (six-week) follow-up visit—15 cases.



For several reasons, it seemed expedient to divide the series arbitrarily into two sections—those performed from 1931 to 1940, and those from 1941 to 1945. This would indicate any progress toward betterment of results or toward improved selectivity of cases. Also, the effect of longer follow-up could be observed.

Before considering results, a brief word is in order about the classification of cases. To be included in the essential dysmenorrhea group, a patient must first have had her dysmenorrhea throughout her menstrual life. A point of particular interest is that very nearly 100 per cent of the records of this group underline the symptom *cramps*. Whatever associated symptoms may have been present, cramps always seemed to be in the foreground. These were severe enough to render the patient at least economically useless during her periods, if not bedridden for the first day or two of the flow. Often one of the tests for acceptability for the operation came to be the question, "Do you have enough discomfort to want an abdominal operation for its relief?"

Second, the pelvic examination had to be negative. A retroversion with retroflexion, some enlargement of the fundus from edema, and broad ligament varices at laparotomy obviously belongs in the acquired group. However, a simple physiologic retroversion without these associated findings was put in the essential group because we see many such instances where dysmenorrhea is not present, and do not consider such cases ones of acquired dysmenorrhea.

Third, the pelvis at laparotomy had to be negative likewise, as well as the pathologic reports of the curettings, biopsies, etc.

The acquired group presents no problem of classification, as will be evident in another section of this report.

Now it is patent that judgment of the degree of relief following presacral neurectomy is subject to wide and individual variation. However, the patients at the two ends of the scale offer no problem. Patients with complete relief will say so and are delighted with the operation. A frequent comment in follow-up letters is, "Everyone should have this operation." Patients who are not helped at all make this fact clear also. The middle group is the difficult one to judge. Therefore, the simplest way appeared to be to tabulate the two extremes and let the middle group separate out as a result. It was feared that there would be a large number of this category, but this did not prove to be the case. Thus, under the two general headings of dysmenorrhea, there developed three categories: those completely relieved, those in whom the operation proved a total failure, and the middle group who obtained some relief after the operation.

### Report of Cases

There were 136 cases performed in the first 10-year period, as summarized in Table I. The period of follow-up varied from six months to fifteen years, with a mean of three years. There were 92 cases followed from one to five years after operation. A certain number proved unsuitable for inclusion in the series for the following reasons.

total failure in 30 cases (41.7 per cent). Thus, while the recent five-year period shows an increase in good results in the essential group of 11.6 per cent over the previous ten-year period, which is gratifying, it also indicates an increase in the poor results in the acquired group of very nearly the same amount (10.1 per cent). However, one may perhaps justify the use of presacral neurectomy in this latter series of patients (with acquired dysmenorrhea), provided he will accept as the ultimate result no better than about a 50 per cent chance of relief.

It should be of interest, now, to examine more closely the intimate pathologic findings in the acquired dysmenorrhea cases, and to apply the three gradings of results to the major contributors of this group.

There were in this series, for the entire fifteen years, 72 such cases. Of these, 26 cases were diagnosed as pelvic inflammation. This was confirmed by microscopic examination whenever tissue was removed for study. These 26 cases represent 36.6 per cent of the acquired group—the largest single contributor. The next largest pathologic entity encountered was endometriosis, with 17 cases, or 24.0 per cent. These two conditions accounted for 60.6 per cent of all the acquired dysmenorrhea coming to presacral neurectomy. What were the specific benefits of the operation in these cases? Table IV brings this out clearly. Only three cases of true pelvic inflammation in which a conservative operation was carried out (together with presacral neurectomy) showed relief. Often such conservatism was demanded by the patient, who wished to be operated upon, but who refused permission for hysterectomy, even if conditions might warrant it. There were 6 of these cases who obtained some relief. As might well be suspected, 17 cases, or 65.4 per cent, derived no benefit as far as their dysmenorrhea was concerned. This represents the largest single group of failures encountered.

TABLE IV. PRESACRAL NEURECTOMY; ACQUIRED DYSMENORRHEA—1931-1945, INCLUSIVE

Total number of cases: 72			
Etiology—Pelvic inflammation		26—36.6%	
Endometriosis		17—24.0%	
Total		43—60.6%	
		Results	
Pelvic Inflammation		Endometriosis	
Complete relief	3—11.5%	Complete relief	7—40%
Partial relief	6—23.1%	Partial relief	5—30%
Total failure	17—65.4%	Total failure	5—30%

In endometriosis, after conservative operative treatment, the picture is more evenly balanced. There were seven such patients relieved, five partially relieved, and only five, or 30 per cent, recorded as failures.

Finally, there remained a miscellaneous group of 28 cases summarized in Table V. Fibroid uterus, as a cause of acquired dysmenorrhea, deserves little comment. Whenever feasible, these myomas were removed, of course. Post-operative adhesions deserve special mention. The majority of these eight cases were in young women who had had a previous appendectomy elsewhere for what was designated, apparently, as "chronic appendicitis." Often, following this, their dysmenorrhea was centered primarily in the right lower quadrant and often omental and pericecal adhesions were found at laparotomy for presacral neurectomy. In most such instances, there was immediate and gratifying relief following the neurectomy. This leads one to speculate as to whether these patients did not have, in the beginning, a somewhat atypical essential dysmenorrhea which was interpreted as "chronic appendicitis," and for which they were operated upon without relief. One has no proof of this, and the cases are thus included in the acquired group.

2. Patients with acquired dysmenorrhea who had a good result at only one follow-up visit—seven cases. (The acquired group, with a poor result, and only one visit were included in the poor-result figures, for it was felt that any subsequent improvement which they might have shown could hardly be attributed to the presacral neurectomy.)

3. Diagnosis of dysmenorrhea inconclusive—three cases. The same remarks made under this heading in the first ten-year group apply here.

4. "Carcinoma-in-situ" of the uterine cervix—one case. This patient was

TABLE II. PRESACRAL NEURECTOMIES—1941-1945, INCLUSIVE

<i>Total number of cases:</i> 119	
<i>Number of cases rejected:</i> 26	
1. Inadequate follow-up	15
2. Acquired dysmenorrhea with good result at only one (6-week) visit	7
3. Diagnosis of dysmenorrhea inconclusive	3
4. Carcinoma-in-situ, cervix	1
<i>Number of cases remaining:</i> 93	
<i>Essential Dysmenorrhea</i>	
59 cases—63.5%	
Complete relief	50—84.6%
Partial relief	4—6.8%
Total failure	5—8.4%
<i>Acquired Dysmenorrhea</i>	
34 cases—36.5%	
Complete relief	10—29.4%
Partial relief	8—23.5%
Total failure	16—47.1%

34 years old, married for fifteen years, with two children. She had had a symptomatic retroversion-retroflexion with disabling backache for one and one-half years. Early preinvasive carcinoma of the cervix was encountered on routine biopsy done at the time of presacral neurectomy, and fifteen days later she was subjected to total hysterectomy. She was last seen Dec. 5, 1945, at which time she was well, and physical examination was completely negative.

The number of cases remaining was 93. In 59 of these (63.5 per cent) essential dysmenorrhea was considered to have been present. In 34 (36.5 per cent) acquired dysmenorrhea existed. Inspection of these cases revealed that in the essential group, this time, 50 cases (84.6 per cent) reported complete relief; four (6.8 per cent) reported partial relief; five (8.4 per cent) were total failures.

In the acquired group, again, the figures reflect the results seen in the earlier period. Of the total of 34 cases, only 10 (29.4 per cent) reported success; eight patients (23.5 per cent) reported partial relief; 16 patients (47.1 per cent) obtained no relief from their dysmenorrhea at all.

Table III summarizes the first two tables for the entire series. Briefly, 255

TABLE III. PRESACRAL NEURECTOMIES—1931-1945, INCLUSIVE

<i>Total number of cases:</i> 255	
<i>Number of cases rejected:</i> 46	
<i>Number of cases remaining:</i> 209	
<i>Essential Dysmenorrhea</i>	
137 cases—65.6%	
Complete relief	107—78%
Partial relief	15—11%
Total failure	15—11%
<i>Acquired Dysmenorrhea</i>	
72 cases—34.4%	
Complete relief	24—33.3%
Partial relief	18—25.0%
Total failure	30—41.7%

cases are represented, with 46 rejected for reasons enumerated above, leaving 209 cases for consideration. In the essential dysmenorrhea series of 137 cases (65.6 per cent), complete relief was afforded in 107 (78 per cent), partial relief in 15 cases (11 per cent), total failure in 15 cases (11 per cent). In the acquired dysmenorrhea series of 72 cases (34.4 per cent of the 209 patients), complete relief was afforded in 24 (33.3 per cent), partial relief in 18 (25 per cent),

Total failure of the procedure was recorded in 11 per cent of the essential dysmenorrhea group, whereas this poor result obtained in 41.7 per cent of the acquired dysmenorrhea group.

The offending pathologic conditions in the acquired cases are reviewed. It is pointed out that pelvic inflammation and endometriosis made up about 60 per cent of this group; 21 per cent of cases in these two categories came to total hysterectomy nine months to four years after presacral neurectomy was performed.

We wish to emphasize that presacral neurectomy is still a court of last resort in the treatment of dysmenorrhea, that the operation carries with it the risks of laparotomy, and that good medical management should be attempted in each individual case before resorting to surgery unless other indications for laparotomy exist.

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Of the remainder of the list, the etiology is evident and needs no further augmentation. The distinction was made earlier between the symptomatic, retroverted, retroflexed, enlarged, boggy uterus responsible clinically for acquired dysmenorrhea, which is rare in this series, and the true physiologic retroversion which we feel is asymptomatic per se, as shown by Meigs,<sup>2</sup> and not responsible for dysmenorrhea of either type.

TABLE V. MISCELLANEOUS CAUSES OF ACQUIRED DYSMENORRHEA COMING TO PRESACRAL NEURECTOMY—1931-1945, INCLUSIVE

Fibroid uterus	7
Postoperative adhesions	8
Postpartum dysmenorrhea	5
Ovarian cyst	3
Acquired retroversion-retroflexion	2
Adenocystoma of uterus	1
Membranous dysmenorrhea	1
Cause not evident	2
Total	29 cases (39.4%)

A final comment on the results in Table IV should be added. Of the 17 cases of failure in pelvic inflammation, seven cases have, to date, come to total hysterectomy nine months to four years after the initial laparotomy. That still more of these may follow is quite possible. Of the five failures in the endometriosis group, two have submitted to subsequent hysterectomy, and one other is on the list awaiting operation. The posthysterectomy results in these nine cases have been uniformly satisfactory.

There was no mortality in the series. There have been no more postoperative complications following presacral neurectomy than one might expect in any group of patients coming to laparotomy for relatively minor pelvic surgery. There is no evidence in this series of any significant alteration in bowel habit, bladder function, or libido. Early in our experience a right ureter was unsuspectingly tied and went undiagnosed for a time. It was later hoped that the affected kidney would atrophy, but, unfortunately, a vigorous pyelonephritis developed in it, necessitating its removal. With the present modification of the method in force, in which the right ureter is identified, freed of its attachments for a short distance over the sacral promontory, and retracted laterally before any attempt is made to develop and excise the plexus, the possibility of such an accident has been eliminated. Perhaps the greatest single danger in the procedure lies in possible laceration of the great veins surrounding the operative site, a catastrophe which might entail heroic measures and which should not occur in skilled and experienced hands.

### Summary

The results of 255 cases of presacral neurectomy for dysmenorrhea of both the essential and the acquired types are reviewed.

A comparative study is made between the 136 cases performed from 1931 to 1940, and the 119 cases from 1941 to 1945.

Complete relief from what is commonly termed essential dysmenorrhea (cramps) was obtained in 78 per cent of cases. There was some degree of improvement of symptoms in a further 11 per cent.

Complete relief from acquired dysmenorrhea occurred in only 33.3 per cent of cases.

All of the patients sought medical aid voluntarily, and complained of pruritus vulvae as the primary symptom. The presence or absence of pruritus was used as an indication of the efficacy of the therapy so far as symptoms were concerned. Forty-nine of the patients were white, and five were Negro. Twenty-four of the patients were pregnant. The duration of symptoms varied from forty-eight hours to five years. Thirty-four of the patients had been symptomatic for one month or longer. Eighteen had received previous therapy which included roentgen ray, infra red light, stilbestrol, bismuth and gentian violet, vaccine, mercurochrome, and a variety of chemicals in the form of ointments and douches. Two of the eighteen patients had acute edema of the vulva, and one patient had cutaneous involvement of the skin surrounding the vulva.

### Symptoms and Physical Findings

The primary complaint of all of the patients was itching of the vulva which varied from minimal to intense. They complained secondarily of irritation and rawness of the vulva with burning on urination. The complaint of discharge was common only in the patients with severe infections. The most frequent physical findings were a cheesy, white, flaky vaginal discharge, and hyperemia of the vaginal mucosa and vulvar areas. In a few patients the hyperemia was accompanied by actual edema. In some of the patients who complained of pruritus the physical findings were within normal limits, and the diagnosis of mycotic vulvovaginitis could be made only by culture.

### Fungi Isolated

All of the fungi isolated were classified according to methods previously described by Jones and Martin,<sup>4</sup> in 1938, and Martin, Jones, Yao, and Lee,<sup>5</sup> in 1937. Fifty-three of the strains were identified as *Candida (Monilia) albicans* and one strain as *Candida (Monilia) stellatoidae*.

### Methods Used

Complete vaginal and vulvar cultures were first obtained to establish the diagnosis. Once the diagnosis was established the patients were treated with the jelly supplied in tubes with an applicator which delivered from eight to 10 c.c. Each patient was instructed to use one applicator full of jelly on arising in the morning and one applicator of jelly on retiring at night. The patients were told to insert the applicator full length in the vagina to deposit the jelly in the upper vagina. They also were asked to apply a small amount of the jelly to the external genitals with their fingers.

Early in the study follow-up cultures were taken daily. It was soon determined that cultures taken within a few days after therapy was started were positive, and that the amount of jelly in the vagina at the time of culture would not seriously influence the cultural results. As a rule, if negative cultures were to be obtained they were not obtained for five to seven days after the therapy was started. After this observation was confirmed, it was decided to treat each patient for a period averaging from two to three weeks. After completion of therapy the patients waited two days, used no douches or medication, and then returned for follow-up cultures. For evaluation of the therapy all patients who at this time had negative cultures, who were asymptomatic, and who had negative physical findings were regarded as cured. Positive cultures obtained weeks or months later were classed as recurrences.

Early in the study the patients were instructed to take a plain water douche before using the jelly. As douches seemed to interfere with the jelly staying in contact with the vaginal mucosa, the patients were restricted to the use of a

## THE TREATMENT OF MYCOTIC VULVOVAGINITIS WITH PROPIONATE VAGINAL JELLY\*

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MYCOTIC vulvovaginitis remains one of the difficult specific vulvovaginal infections to control or eradicate, despite the number of reported methods of treatment. The majority of the treatments is time-consuming for the physician or seriously objected to by the patient. The most commonly employed method of treatment is the use of 1 per cent aqueous gentian violet applied to the cervix, vagina, and vulva two or three times weekly. When used in this manner, gentian violet cannot be applied adequately by the patient, and chemical reactions are common.

The use of the propionates was suggested by Keeney and his co-workers<sup>1</sup> in 1944 in an article on the fungistatic and nontoxic properties of the propionates. One of us (R. L. A.) prepared a jelly-like mixture of 20 per cent, equal parts, of calcium and sodium propionate in a tragacanth base, and buffered at a pH of 6.5. This was the pH at which the fungicidal action was most active in vitro for *Candida (Monilia) albicans*. The results were most encouraging. We continued searching for the most satisfactory vehicle, and have worked out the formula of a jelly† which fulfills most of the necessary requirements. Work is still in progress to improve the jelly and the methods of treatment.

### Material

For the past two years we have treated all patients with mycotic vulvovaginitis with some form of vaginal jelly. From this group 54 patients were eligible for this report after adequate observation. All of the patients selected had positive cultures for some species of *Candida*. Carter and Jones,<sup>2</sup> in 1937, obtained positive cultures for yeastlike fungi from 32 per cent of 114 pregnant patients, and from 14 per cent of 100 apparently normal gynecologic patients. However, as Carter, Jones, Ross, and Thomas<sup>3</sup> pointed out in 1939, it is only the yeastlike fungi belonging to the genus *Candida* which produce symptoms. Although yeastlike fungi belonging to the genera *Saccharomyces* and *Cryptococcus* were frequently found, no symptoms were present in patients who harbored these fungi.

No patients were included in the present study who had mixed infection or who had other vulvar conditions which might conceivably produce symptoms.

\*Part of the expense incurred in this study was defrayed by a grant from the Research Council of Duke University.

†Propion gel, prepared by the Mycoloid Laboratories, Inc., Little Falls, N. J.

Formula—Calcium propionate	9.5%
Sodium propionate	9.5%
Propionic acid	1.0%
Glycerine	10.0%
Bentonite	32.0%
Water	39.0%

### Comment

In our experience, the propionates in a vaginal jelly offer definite advantages over other forms of treatments available. The jelly has the added advantage of causing no chemical irritation or sensitivity reactions so frequently seen in the use or misuse of other agents. Furthermore, the jelly can be used without the necessity of frequent office visits, and it does not stain the patients' clothing.

It is obvious that the perfect treatment for mycotic vulvovaginitis has not been found. This is evidenced by the low percentage of "culture" cures in the obstetric patients whose lower genital tracts provide such satisfactory environments for the fungus growth. Even though cultural cures cannot be effected routinely in these obstetric patients, symptomatic relief can be secured without fear of ill effects.

### Conclusions

1. A new treatment for mycotic vulvovaginitis is suggested.
2. Fifty-four patients with mycotic vulvovaginitis were treated with a vaginal jelly containing calcium and sodium propionate as the active ingredients.
3. All of the patients received relief from pruritus vulvae within seventy-six hours.
4. Eighty per cent of the nonpregnant patients and 39 per cent of the pregnant patients were cured of the infection, as proved by culture, by one series of treatments.
5. The jelly is entirely innocuous, convenient to use, and does not stain the clothing.

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single douche at the beginning of the treatment. The treatment was purposely simplified to make it practical for the physician and the patient. Undoubtedly, were a more vigorous treatment regime followed, results would improve accordingly.

### Cooperation of Patients

Obviously, in any treatment of this type the degree of cooperation of the patients is extremely difficult of evaluation. That was certainly true in these patients. It soon became clear to us that the patients found certain distasteful aspects to all vaginal therapy, and that some patients used the jelly only to the extent of relieving symptoms. Since we believe that the same problem will be encountered when testing any vaginal preparation, we are including these patients without further comment or explanation.

### Toxicity of the Jelly

No reactions of any type have been noted. A few patients with a number of recurrences have used the jelly sporadically over a period of eight to ten months without irritation of any kind. Many of the patients complained of a burning sensation immediately after the first two or three applications of the jelly. In all patients this stopped as the jelly was continued. It was found that the burning was dependent upon the amount of irritation and excoriation present and that the patient did not object if informed before the treatment was started that burning might occur. Some of the patients complained that the jelly was "messy." These were usually patients with mild symptoms. Reducing the amount of jelly to permit less to work its way to the vulva helped correct this complaint. We felt however, that jelly on the vulvar tissues was an essential part of the treatment.

TABLE I

	24 HR.	36 HR.	48 HR.	76 HR.	NOT KNOWN BUT WITHIN 76 HR.
Relief of pruritus vulvae obtained in approximately	16	5	18	6	9

### Results

All of the patients received relief from pruritus within seventy-six hours. The average time of symptomatic relief is given in Table I. The results of follow-up cultures on both the gynecologic and obstetric patients are shown in Table II. Of 30 nonpregnant patients, 24 showed negative cultures after one series of treatments. Four of the six failures were classed as failures either because the patients did not return for culture or the observer failed to obtain a culture. Two of the six failures had positive cultures even though they were entirely asymptomatic. These two patients were willing to use the jelly only long enough to obtain relief from the itching. Five of the 25 patients classed as cures had a recurrence of symptoms within two to six months.

As shown in Table II, all of the pregnant patients obtained symptomatic relief as readily as the nonpregnant patients, but the percentage of negative cultures obtained was considerably lower than in the gynecologic patients.

TABLE II

	CULTURE CURES	CULTURE FAILURES	RECURRENCES
Gynecologic patients	24	6	5
Obstetric patients	8	16	1

ovary and tube adherent to the broad ligament and peritoneum . . . left ovary also adherent but small and superficially cystic."

*Pathologic Findings.*—

*Gross:* The specimen submitted was that of the supracervical portion of the uterus with both tubes and ovaries attached, and an accompanying appendix. The uterus measured 8 cm. by 6 cm. by 6 cm., and was of uniform consistency and symmetrical in shape. The myometrium was without distinct gross change. The endometrium was uniform, 8 mm. in thickness, very soft, pale, moist, and glistening. The attached tubes and ovaries were covered by multiple fibrous adhesions. The right ovary measured 5 cm. in length. It had a granular scarred external surface showing adhesion tags. On section, glistening white finely granular lobulated nodular tissue was found. This formed a sharply circumscribed nodule measuring 2.5 cm. in diameter. The tissue itself on manipulation had many fine granular elevations and distinct fissures.

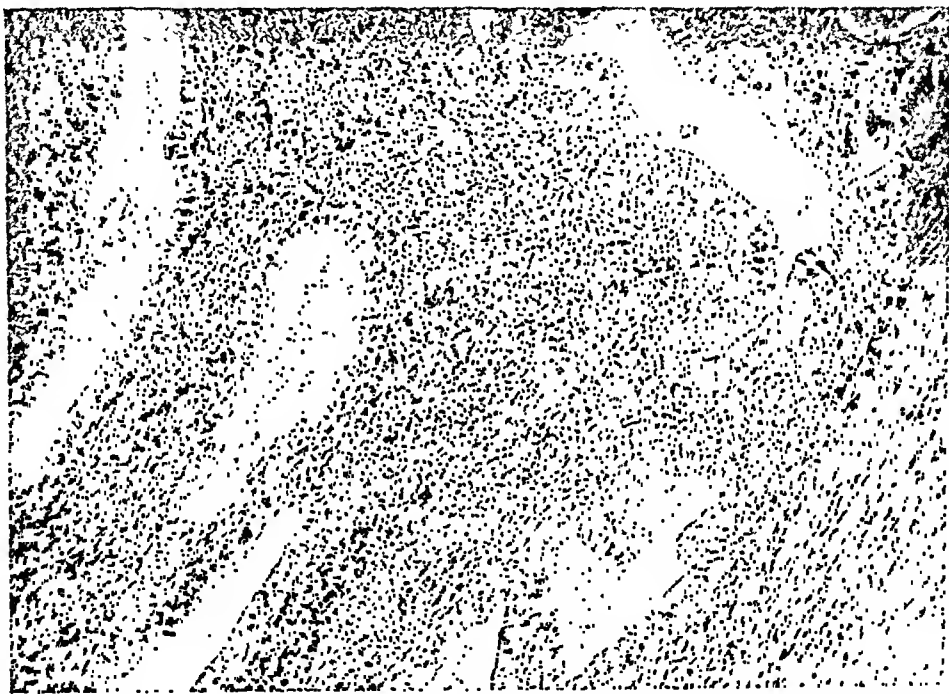


Fig. 1.—(×300.) Case 1: Photomicrograph of ovary with endometriosis. Well-developed endometrial glands accompanied by abundant endometrial stroma form the major portion of the photograph.

One part of the nodule contained yellowish granular material. The left ovary was 4 cm. in length. It had a central hemorrhagic cyst measuring 1.5 cm. in diameter. The cyst was outlined by brownish granular material firmly attached to a granular internal surface. The tube was deeply congested, but soft and pliable. The accompanying appendix was 7 cm. in length, and had no surface changes.

*Microscopic:* The endometrium showed an edematous swelling with pale staining spongy type of stromal tissue. The glands were long, moderately tortuous, and showed subnuclear vacuolization. The glands were quite uniform in cellular outline. Minute foci of lymphocytic cells were present.

The myometrium was without particular change.

The left ovary presented a rather prominent brownish granular pigmentation in which much of the pigment was contained in macrophages. The cystic area was outlined by columnar epithelium and columnar glands which gen-

## OVARIAN ADENOACANTHOMA ASSOCIATED WITH ENDOMETRIOSIS OF THE OVARY

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THE tumor called adenoacanthoma or adenocarcinoid is of rare occurrence. It was in 1907 that Herxheimer<sup>1</sup> first reported on the occurrence of this type of tumor. The name is derived from the designation of the tumor's histologic composition which is a mixture of glandular elements and squamous epithelium. The relationship of these two elements is so intimate that portions of glands as well as interglandular substance may be formed by squamous epithelium. The occurrence of the adenoacanthoma is most often seen in the uterus wherein the incidence is approximately 3 per cent. However, other cases have been reported as arising principally from the gastrointestinal tract.

The occurrence of adenoacanthoma in the ovary has been extremely rare. The first two cases recorded are mentioned by Meigs<sup>2</sup> as being metastatic tumors of the ovary from a primary adenoacanthoma of the corpus uteri. Dockerty<sup>3</sup> has also seen such a case. In 1944 Simpson and Branch<sup>4</sup> reported a possible case of adenoacanthoma of the ovary which, however, was diagnosed as a Brenner tumor by several outstanding gynecologic pathologists. The first two primary cases, according to a survey of the literature available to the author, were reported by G. F. Melody and his associates<sup>5</sup> in 1945. They encountered adenoacanthoma development of the ovary in two patients, one a 69-year-old white woman, and the other a 61-year-old Negro woman.

The two cases reported herein are those of women in the reproductive period of life who have had clinical symptoms and pathologic findings of endometriosis of the ovaries. The association of the endometriosis and the adenoacanthoma of the ovaries is so intimate as to suggest a definite causal relationship.

### Report of Cases

CASE 1.—Mrs. G. T.: service of Dr. A. Mayfield, St. Catherine's Hospital, Kenosha, Wisconsin. The patient was a well-developed, well-nourished, 42-year-old white woman, gravida iii, para iii. She presented herself in April, 1946, with the chief complaints of pelvic pain, tenderness, and the feeling of weight and fullness in the pelvis for twenty-two years, following the birth of her last child. This began as mild intermittent discomfort, which gradually increased over the period of years. In the past two years it had progressed to such an extent that it was disabling. In the past four years this was accompanied by moderate leucorrhea, but no intermenstrual bleeding. Menstrual history was normal with the exception of moderate dysmenorrhea. On physical examination, the essential findings were limited to the pelvis. The findings were those of a scarred cervix, normal sized and normal positioned uterus, and the finding of fullness and resistance in the right adnexal area. The left adnexal area was negative. A laparotomy was performed with a subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy. Surgeon's note: "At the time of operation uterus normal size . . . right ovary three times normal size having a cyst filled with brownish fluid . . . right

erally had basilar nuelei, but in many areas the nuelei were pseudostratified. The free portions of the cells had prominent cytoplasm. This epithelium was accompanied by a pale staining spongy round cell and stellate cell endometrial stromal tissue. Free red blood cells were found in the stromal tissue and in many of the small accessory glands.

The right ovary also had evidence of some granular brownish pigment present in macrophages. The main portion, however, showed a glandular formation. This was characterized by large irregular tortuous columnar glands which had basilar nuelei and a light pink staining, at times vesicular, cytoplasm. Portions of the glands in some instances were outlined by a squamous type of epithelium. In such instances the squamous epithelium continued between the glands, forming small nests and whorl-like structures. Some of the cell nests were rather large, and the centrally located nuelei were swollen, eosinophilic in staining property, and in some cases represented by a light reddish staining hyaline appearing disc. Mitoses were very scant. The squamous epithelium was followed as a process of metaplasia which was rather distinctly exemplified in many areas.

*Diagnosis.*—Glandular hyperplasia of the endometrium; chronic appendicitis; ovarian endometriosis; adenoacanthoma of the right ovary.

CASE 2.—Miss M. W.; service of Dr. F. Hofmeister, Milwaukee Hospital, Milwaukee, Wisconsin. The patient was a 36-year-old, unmarried, well-developed, well-nourished, white woman who entered the hospital in May, 1946, with the chief complaints of abdominal tenderness, backaches, menorrhagia, constipation, dysmenorrhea, and leucorrhea. These symptoms had an insidious onset in the latter part of 1945. The pain experienced was described as being located in the right lower quadrant and in the umbilical region. In the past three to four months the previously normal menstrual periods had become longer and more profuse. There was no relevant past history. Physical findings were limited to the pelvic examination. This was attended by pain and the finding of bilateral cystic ovaries with some fixation of the left adnexa. The uterus was normal in size. The patient was operated upon, with a preoperative diagnosis of "cystic left ovary the size of a grapefruit, possible endometriosis, and possible cyst of the right ovary." Pathologic findings at the time of laparotomy were those of "extensive endometriosis of the left ovary, cul-de-sac, and rectosigmoid, with obliteration of the cul-de-sac; multilocular cyst of the left ovary the size of a large grapefruit; and fibroid of the uterus." Bilateral salpingo-oophorectomy, total hysterectomy, and appendectomy were done.

#### *Pathologic Findings.*—

*Gross:* No tissue of cul-de-sac was received. The uterus measured 12 cm. by 9 cm. by 6 cm. It contained a 5 cm. sharply circumscribed white nodule composed of whorls. The endometrium was thickened and polypoid in character. It, however, was soft and glistening. The right ovary contained a hemorrhagic corpus luteum cyst and a follicular cyst. The ovarian substance was soft and edematous, but the cortex was thick and covered by adhesions. The left ovary measured 9 cm. in diameter. It was a glistening cyst that had one furrowed surface wherein there was fine granularity and attached hemorrhagic fatty tissue in the nature of adhesions. On opening the cyst, the wall varied in thickness ranging from 3 to 10 mm. It contained a brownish cloudy fluid. Most of the cyst wall was covered on the internal surface by pasty brownish granular material; however, in one area, which corresponded to the surface depression, there was a papillary very soft pink growth measuring 3 cm. in width and 1.5 cm. in thickness. On section through this area the granular papillary material extended through the thickness of the cyst

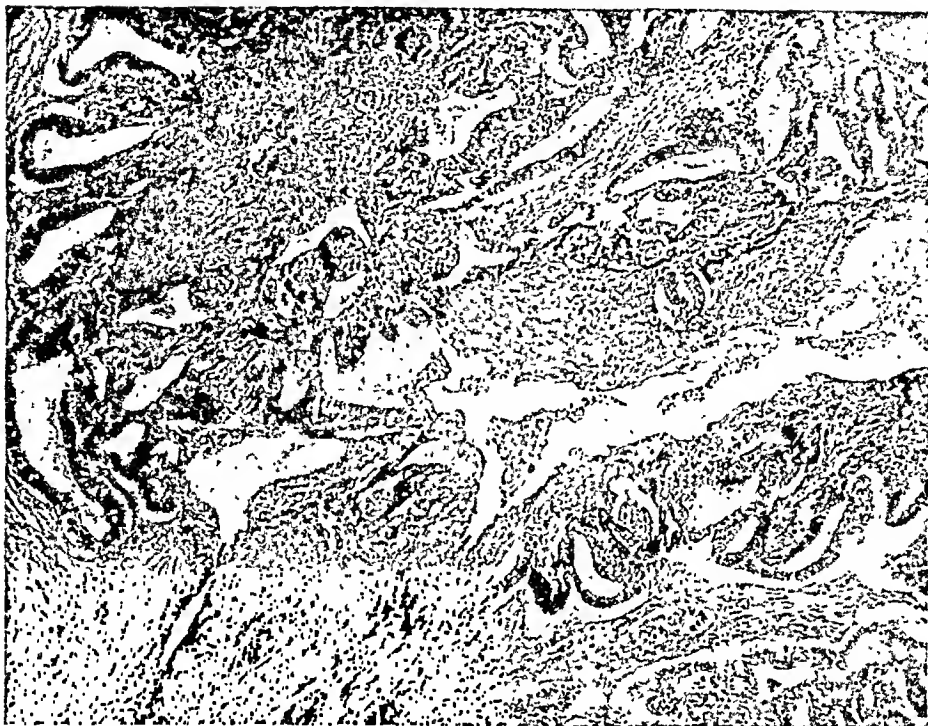


Fig. 2.—( $\times 40$ .) Case 1: Photomicrograph of adenoacanthoma of the ovary showing well-developed columnar glands which are accompanied by large nests of squamous epithelium. The masses of squamous epithelium form portions of the gland outlines.

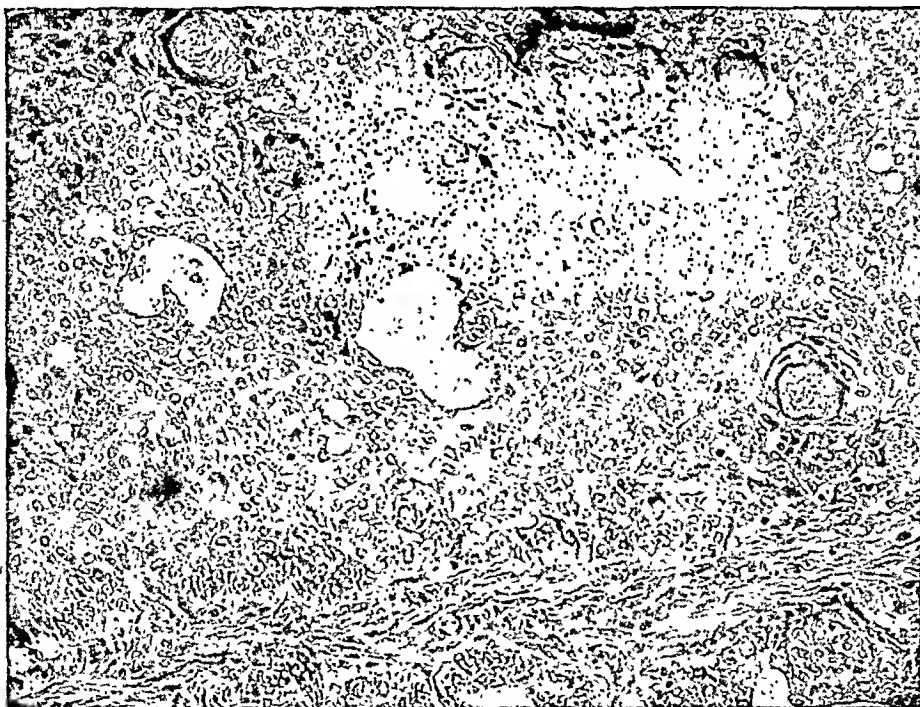


Fig. 3.—( $\times 300$ .) Case 1: Photomicrograph of a mass of squamous cell metaplasia occurring in the adenoacanthoma. In the lower portion of the photograph are parts of columnar glands. The remainder is a mass of squamous epithelium showing numerous discs of keratin material.

The right ovary presented surface adhesions in which there were many dilated vascular channels. A few histiocytes and lymphocytes could be seen in the adhesions. These adhesions had formed irregular cleftlike spaces which were outlined by the mesothelial cells of the ovarian surface. This ovary had foci of pigment laden macrophages surrounded by dense hyaline tissue.

The tube section showed moderate thickening of the folds of the endosalpinx. The wall was moderately hyperemic and showed minute collections of lymphocytes. The surface of the tube presented a glandular structure outlined by columnar epithelium and some swollen elongated cells about the periphery. The gland was accompanied by hemorrhage and some polymorphonuclear cells.

The endometrial particles removed by curettage showed general glandular hyperplasia. The stroma varied in consistency. In many places it was edematous and partially hemorrhagic. Some areas showed compact stroma containing minute lymphocytic foci. In two small particles of endometrium the glands were closely spaced. Here were evident minute foci of metaplasia in which there was squamous type of epithelium, somewhat like that seen in the ovary. However, these were microscopic foci in which only a few cells formed the metaplastic squamous cell aggregates that lay within the individual glands.

*Diagnosis.*—Polypoid glandular hyperplasia of the endometrium showing a microscopic focus of adenoacanthoma; endometriosis of the tube; papillary cyst adenoacanthoma of the left ovary; fibroleiomyoma; old hemorrhagic cysts of the ovary, probably endometriosis.

### Discussion

The development of adenoacanthoma in these two cases is associated with ovarian endometriosis. In Case 1 this is unquestionable from the standpoint of gross and histologic findings. In Case 2 the findings at surgery were excellent, but the histology is not nearly as convincing; however, the ovarian changes in reference to the old brownish pigmentation and the small chocolate cyst areas can readily be interpreted as inactive endometriosis. The interpretation of adenoacanthoma development in endometriosis, at least in Case 1, is concurred by Hertig.<sup>6</sup> Dockerty<sup>3</sup> states that he has encountered such cases but has not been able to prove definitely the relationship of adenoacanthoma development in ovarian endometriosis; however, in one of his cases he mentions previous surgery, hysterectomy, for endometriosis. Likewise, it may be reasonable to interpret other ovarian neoplasms as arising from unrecognized endometriosis; since histologically the pattern is often so typical of endometrium.

In Case 2 the finding of a microscopic focus of adenoacanthoma in the corpus in all probability represents a separate tumor development in a very early stage, or it may even be interpreted as a metastasis from the larger and more definite adenoacanthoma of the ovary. However, the metaplasia in the endometrium is so well defined and limited to normally existent endometrial glands that metastasis is probably not the explanation. That such a case should have endometrial changes similar to the ovarian changes is not unusual if one considers the presence of endometrium in both areas (corpus uteri and endometriosis of the ovary). Certainly ovarian endometriosis participates in the function of menstruation. Whatever the influence, it may well be active in all places wherein endometrium is found.

The development of adenoacanthoma in the ovary as a process of metastasis, however, is cited by Meigs<sup>2</sup> and Dockerty.<sup>3</sup> The two cases reported by Melody<sup>5</sup> are neither metastasis from the uterus nor associated with endometriosis. Ewing<sup>7</sup> discusses the mechanism (metaplasia, cell rests, independent



wall and was the cause of the surface adhesions. Other portions of the cyst wall contained flattened cysts ranging from 3 to 8 mm. and filled with a thick pasty chocolate material. The tubes were soft, congested, and uniform. There were a few fragments of endometrial tissue also submitted.

*Microscopic:* Left ovary—The cyst wall was dense fibrous tissue substance which had an internal lining of many pigment laden macrophages. The papillary formation visible grossly was seen to be a glandular papillary formation. This was composed of tall columnar irregular sized glands which had produced a very light pink staining secretion. The nuclei were vesicular and generally basilar in position; however, many of the glands had nuclei at various levels.

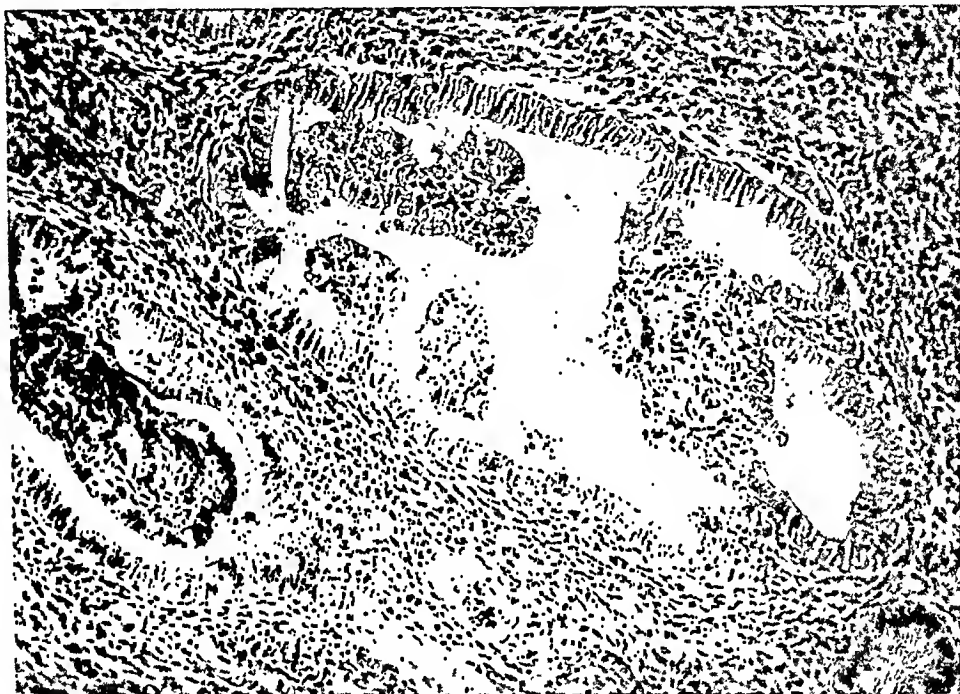


Fig. 4.—(×300.) Case 2: Photomicrograph of endometrium showing well-developed endometrial glands with intraluminal proliferations that have foci of squamous epithelium. The changes are well defined, and there is no disorganization of the glandular pattern of the endometrium.

The free portion of the cytoplasm was rather distinct and marked by small tufts and globules of secretion. Some of the glands were only partially outlined by columnar epithelium, the remainder of the wall being formed by an altered epithelium having the morphologic appearance of squamous cells. This partially outlined many of the glands and formed small whorls and sheaths between the glands. These cells demonstrated reddish granular keratin formation. This was generally found in the center of the cell nests, and ranged from very fine pink staining granularity to very distinct reddish granular discs. Some of the granular discs were punctuated by minute bluish-black granules. These epithelial elements were seen extending onto the external surface of the cyst. Mitoses were present. The cyst lining distant from the papillary formation presented a single layer of tall columnar cells resting on a layer of pigmented macrophages. Areas of this columnar epithelium showed complete metaplasia into squamous epithelium. This was distinct from the papillary glandular architecture of the adenoacanthoma. The smaller cyst structures within the wall of the large cyst showed blood pigment collections outlined by a layer of pigment laden macrophages.

## RECOGNITION OF MIDPELVIC CONTRACTION

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ALTHOUGH pelvic contraction was recognized at least as early as the sixteenth century, it was not until 1861 that Litzmann<sup>6</sup> set forth practical criteria for evaluating the inlet. Outlet contraction, mentioned occasionally through the years, received serious attention only after Williams' exposition,<sup>11</sup> almost fifty years later. There has been a similar delay in the general acceptance of the concept of midpelvic contraction. Although occasional reference has been made to the obstetric significance of the pelvic midplane for at least fifteen years, the subject continues to receive scant attention, and the majority of recent writers ignore it. A single paragraph on the effect of "prominent ischial spines" appears in one of four standard obstetric texts. It is strange that midpelvic capacity should be ignored or its importance denied, since for years this level has been known as "the plane of least pelvic dimensions." Published reports, on the contrary, indicate that interspinous measurements below the generally accepted normal of 10.5 cm. are relatively common. By manual mensuration, Hanson<sup>5</sup> found 16.1 per cent of 1,120 obstetric patients with interspinous diameters 9.5 centimeters or less, using a specifically designed instrument. Others<sup>2, 3, 7, 10</sup> have repeatedly called attention to the frequency of midpelvic contraction.

Obviously, one would expect to find midpelvic contraction in association with contracted inlet and outlet. On the other hand, it can occur with normal inlet and outlet, according to the criteria of Litzmann and Williams. The difference between average pelvic measurements and those at the lower limits of normal demands emphasis at this point. With average manual measurements, it is doubtful that midpelvic dystocia will result. With manual measurements at the lower limits of normal, serious, and even insurmountable midplane disproportion is not only possible theoretically, but also actually does occur, as exemplified by the ensuing report:

F. M., hospital number W-21701, a 33-year-old Negro primigravida, was first seen on January 22, 1945. The pelvic measurements, although small, were within normal limits. As obtained in the outclinic, they were: (inlet) interspinous 25.0 cm., intercrystal 26.5, external conjugate 19.0, diagonal conjugate 11.75 (outlet) bisischial 8.5, posterior sagittal 8.0, and anteroposterior 11.5 centimeters. On the basis of these measurements, delivery by the vaginal route was chosen. She was admitted in active labor on June 16, 1945, with the cervix almost half dilated and nearly effaced, the membranes ruptured, and the vertex engaged and presenting in left occipito transverse position. Cervical dilation progressed to 8 centimeters during the next two hours, but was not completed until fifteen hours later despite adequate uterine contractions. During this time, the fetal heart tones became inaudible. Moreover, there was practically no additional descent of the vertex, which was arrested two fingerbreadths be-



multiple foci) that may be active in the development of an adenoacanthoma. In the two cases herein reported, the squamous cell formation is considered a process of metaplasia.

### Conclusions

1. Two cases of rare adenoacanthoma of the ovary are recorded.
2. Development of the adenoacanthoma is associated with ovarian endometriosis in both cases.
3. The development of squamous cells in these cases is a process of metaplasia.
4. It is suggested that ovarian endometriosis may become a malignant neoplasm.

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spinous ligament, forming the lower limits of the sacrosciatic notch. Average midpelvic measurements may be accepted as follows: transverse (interspinous) 10.5 cm., anteroposterior (from the lower border of the symphysis to the fourth to the fifth sacral interspace) 11.5 cm., and posterior sagittal (from the midpoint of the interspinous line to the same point on the sacrum) 5.0 centimeters. There is no satisfactory method of manual mensuration of midplane diameters. Hanson,<sup>4</sup> in 1930, devised an internal pelvimeter for measuring the interspinous diameter, but the instrument has not received wide recognition. The anteroposterior diameter can be measured in a fashion similar to that employed for the diagonal conjugate of the inlet, namely, by vaginal examination, but the posterior sagittal of the midplane can be measured only by radiographic means.

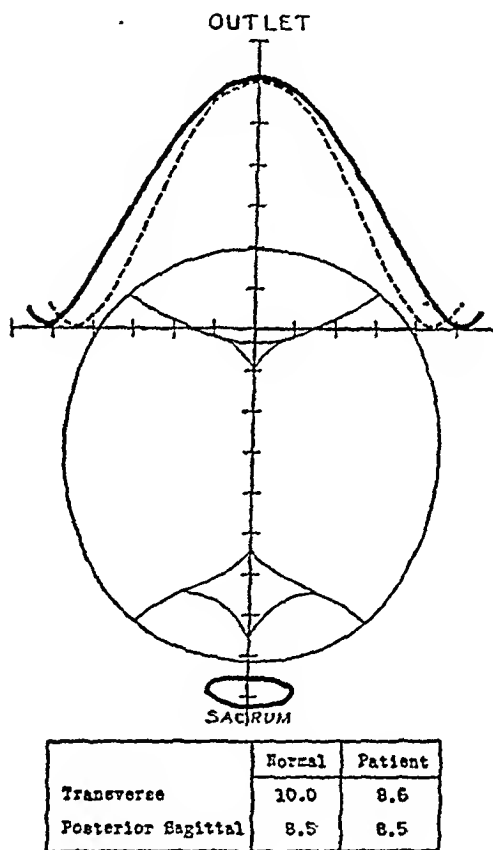


Fig. 3.—Outlet planes of the patient of Fig. 1. The outlet is adequate.

### The Contracted Midpelves

Obviously, midpelvic contraction may be produced by reduction of either the transverse or anteroposterior dimensions, or of both. Transverse narrowing results from two factors: prominence of the ischial spines, and narrowing of the space between the lateral pelvic walls. These factors may augment or nullify each other. Thus, there are four possibilities: widely separated or closely approximated walls, each with either insignificant or prominent spines. Nevertheless, for practical purposes, the critical measurement is the interspinous, since this is always the shortest transverse diameter. Anteroposterior

low the spines. Sudden depression of the blood pressure to 80/60 from previously normal levels motivated decision to deliver after application of restorative measures. A very difficult and traumatizing extraction following craniotomy was necessary to effect delivery, and resulted in a bladder perforation unrepaired at the time because of the patient's precarious condition. The assembled fetal parts weighed 3,134 grams. The puerperal course was uneventful except for a vesicovaginal fistula 4 millimeters in diameter. After the event, roentgenographic mensuration revealed a severely contracted midpelvis, as depicted in Figs. 1, 2, and 3. Had this knowledge been available before the onset of labor, it is probable the patient would have been delivered by the abdominal route, despite antepartum engagement of the head.

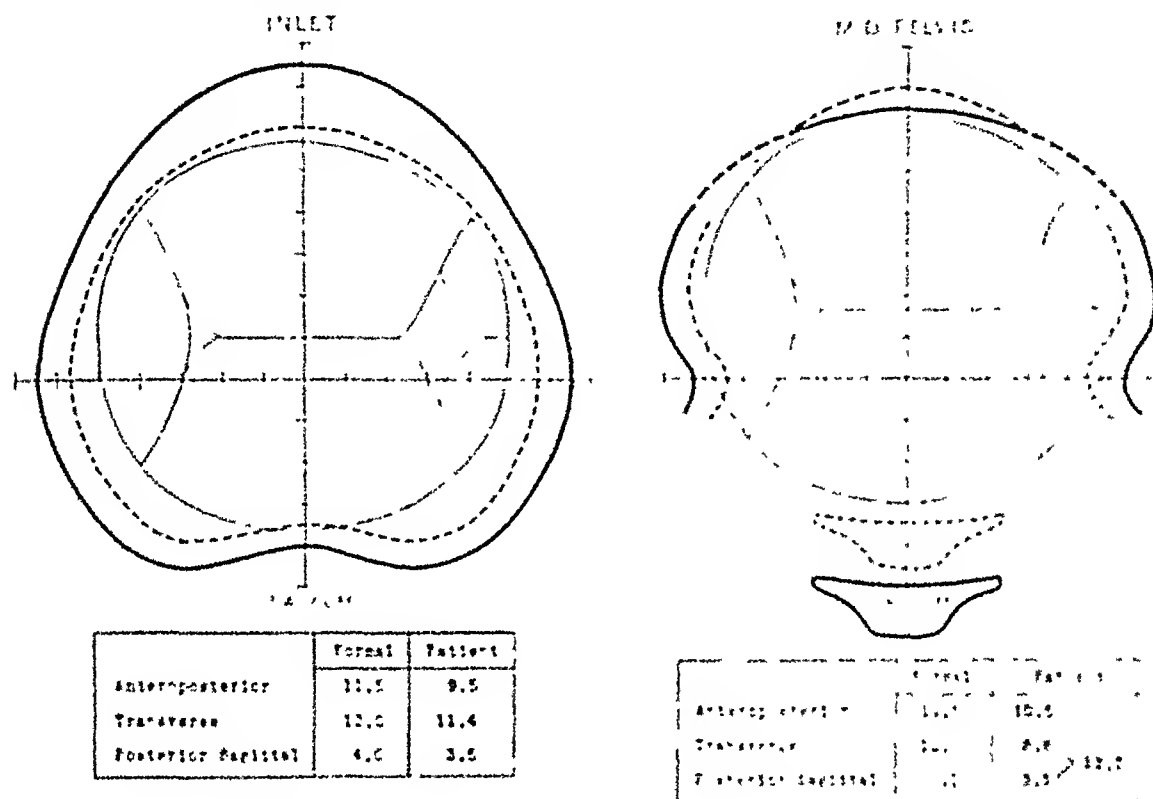


Fig. 1.—Generally contracted inlet. The fetal head can enter with a 9 cm. transverse diameter. The fine lines are drawn to the same scale as the bold line and represent the inlet of an infant weighing between 2,600 and 2,750 grams. The child is a member of the 10 per cent group weighing 3,134 grams. Despite apparent deep position, the head could not enter the inlet. Graduations on the bold lines are 0.5 and 1.0 cm. respectively.

Fig. 2.—The midpelvic plane of the patient of Fig. 1. It is shown that the fetal head passes the midpelvic plane either obliquely or directly transversely.

## The Midpelvic Plane

For obstetric purposes the plane of the midpelvis extends from the inferior margin of the symphysis pubis, passes through the ischial spines, and touches the sacrum in the neighborhood of the junction of the fourth and fifth vertebrae, according to individual sacral conformation (Fig. 4). This is essentially identical with the anatomic description which places the posterior limit at the tip of the sacrum. The inter-punus line divides the midplane into anterior and posterior portions (Fig. 3). The former is bounded anteriorly by the inferior margin of the symphysis pubis and laterally by the ischial spines. The latter portion is bounded posteriorly by the sacrum, its lateral limits being defined by the

contraction involves separate consideration of the fore and hind midpelvis. With sufficient decrease in the interspinous diameter it is apparent that the bulk of the fetal head must pass either anterior or posterior to the spines. Occasionally the forepelvis may be so rounded and deep as to permit descent or rotation anterior to the spines. This, however, is rare since transverse midpelvic contraction is frequently associated with a narrow, angulated and obstetrically useless forepelvis. Caldwell, Moloy, and D'Esopo<sup>2</sup> emphasize that the fetal head usually traverses the hindpelvis. It is precisely for this reason that the posterior sagittal measurement is important, and in this respect, the midpelvis is analogous to the outlet. Evaluation of midpelvic capacity, therefore, depends primarily upon consideration of the interspinous and the posterior sagittal dimensions as emphasized by Guerriero and his associates.<sup>3</sup>

### Recognition of Midpelvic Contraction

As noted above, there is no satisfactory manual method for evaluation of the midpelvis. With careful palpation, it may be ascertained that the spines are prominent, the side walls converge, or the sacrospinous notch is narrow. These findings may occur with adequate midpelvic dimensions and may, therefore, lead to erroneous impressions. On the other hand, dangerous reduction of midpelvic capacity may pass unrecognized by palpation.

Adequate recognition of midpelvic contraction demands roentgenologic mensuration. In a certain sense, this is unfortunate because of indifference or antagonism to roentgenographic pelvimetry in certain quarters. There are two chief reasons for failure of widespread acceptance: (1) technical difficulties of many of the methods currently employed preclude general use; and (2) roentgenologists have often invaded the domain of obstetrics and ventured wholly unjustifiable opinions concerning the prognosis of labor, ignoring such variable factors as size and malleability of the fetal head, and the force of uterine contraction. Both of these objections are minimized by the method of pelvimetry described by Snow and Lewis<sup>9</sup> in 1940. Exposure of the films, a flat anteroposterior and a lateral view, is simple and requires no special equipment. Measurements corrected for distortion can be obtained in a few minutes with a specially devised slide rule. This method combines simplicity, speed, and accuracy, and is available for use by any practitioner willing to spend the few hours necessary to master the technique, and places interpretation of the films in the hands of the obstetrician, where it belongs. Paraphrasing Baptisti,<sup>1</sup> "the obstetrician can master the technique of roentgenologic pelvimetry in a comparatively short time, but the roentgenologist cannot become an obstetrician in that same short time."

### Indications for Roentgenographic Pelvimetry

Obstetricians, recognizing the worth of accepted manual methods of pelvic evaluation, may resent the implication that these methods should be discarded in favor of roentgenographic pelvimetry. Certainly, complete reliance on roentgenographic pelvimetry to the exclusion of obstetric common sense invites serious

PELVIC PLANES

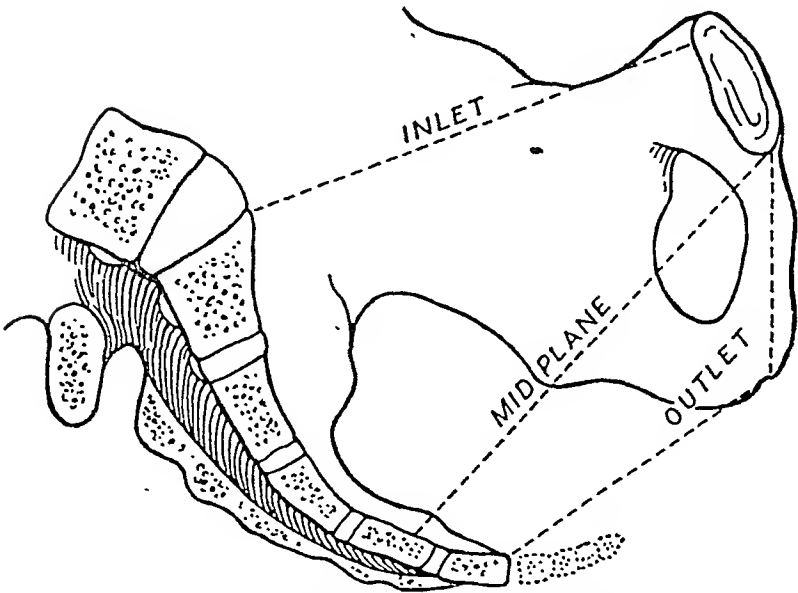
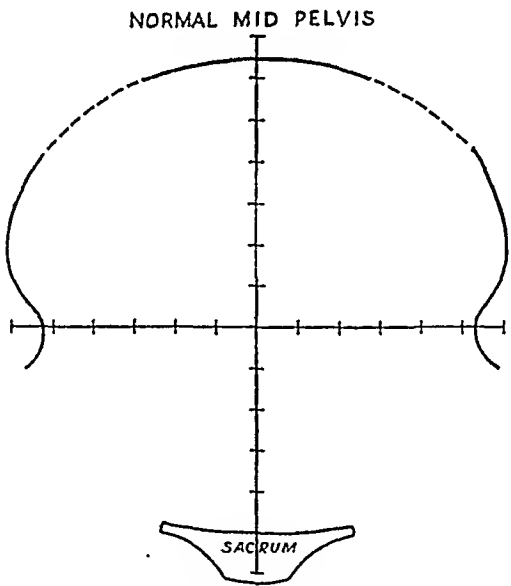


Fig. 4.—The principal pelvic planes. Reproduced from Mengert, W. F.: *Postgraduate Obstetrics*<sup>3</sup> by courtesy of Paul B. Hoeber, Inc.



Anteroposterior	11.5
Transverse	10.5
Posterior Sagittal	5.0

Fig. 5.—The normal midpelvic plane. The interischial line divides the midplane into a fore and hind portion.

To date, no one has published data on a sufficient number of patients to enable formulation of definite criteria. The most acceptable suggestion has come from Guerriero and associates<sup>3</sup> that when the sum of the transverse and posterior sagittal equals 13.5 cm. or less, dystocia may be expected. If a sufficient number of clinics study the problem, principles of management based on accurate antenatal determination of midpelvic capacity will soon be formulated. Then, unforeseen midpelvic arrest, unexpectedly difficult midforceps operation, and unexplained stillbirth and neonatal death due to midpelvic contraction will become infrequent.

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criticism. Equally reprehensible is failure to employ acceptable roentgenographic methods when indicated. Manual evaluation of the obviously adequate pelvis does not need to be supplanted by routine x-ray pelvimetry. On the other hand, manual evaluation of the borderline pelvis should be supplemented by further roentgenographic study.

Therefore, it would be advantageous to set forth criteria of suspicion indicating the necessity for employment of roentgenologic mensuration. To this end, the following didactic rules are suggested with the hope they will serve as a guide toward increased recognition of midpelvic contraction.

Roentgenographic pelvimetry is indicated in the presence of any one of the following:

A. History

1. Difficult labor, especially midforceps delivery.
2. Unexplained stillbirth.

B. Palpation

1. Prominent ischial spines.
2. Sacral deformity. Any, but especially forward angulation.

C. Manual mensuration.

1. Inlet

- a. Ability to touch sacral promontory on vaginal examination.
- b. External measurements below average, i.e., interspinous 23 centimeters or less, intercrystal 26 centimeters or less, external conjugate 17 centimeters or less.

2. Outlet

- a. Bisischial 8.5 centimeters or less.
- b. Sum of bisischial and posterior sagittal 15.0 centimeters or less.

D. Nonengagement of fetal head at term in a primigravida.

Hand in hand with a high index of suspicion of midpelvic contraction, and equally important to the obstetrician, is the conviction based on office methods that a given pelvis is normal. With average inlet measurements (intercrystal 29, interspinous 26, external conjugate 20, centimeters), inability to touch the sacral promontory on vaginal examination, average outlet measurements (bisischial 9.5 plus centimeters), and no palpatory findings or obvious history as enumerated above, the obstetrician is justified in concluding that no serious midplane contraction exists. In such patients roentgenologic mensuration is unnecessary.

### Discussion

Obviously, maximal experience with the incidence and extent of midpelvic contraction can be most rapidly gained by the universal employment of x-ray pelvimetry. Since this is not always practicable, suggestions are made in the present paper whereby midpelvic contraction can be suspected by current manual methods. The obstetrician is thus enabled to isolate a relatively small group of patients most likely to present midpelvic contraction. These patients can be submitted to further study with the roentgen ray. When this is done, it will obviously be convenient to measure all diameters of the three pelvic planes from the films. Previous experience of others leaves no doubt that midpelvic contraction is neither infrequent nor innocuous, and that it may produce dystocia.

technique as a criterion of the responsiveness of the patient to the administration of estrogen, progesterone, and the antiestrogenic materials. As a routine, no patient whose preliminary evaluation indicates the need of gonadotropic stimulation receives it until the use of the estrogens and progesterone has produced a satisfactory vaginal smear, thus warranting gonadotropic therapy.

Many of our patients do not show sufficient physiologic response to substitution therapy to justify the administration of gonadotropic hormones; however, those whose vaginal cornification levels improve enough, do receive equine gonadotropic hormones. In essence, this amounts to a very careful selection of cases, and undoubtedly accounts for the high percentage of good results herein reported.

Long ago, Dunn<sup>4</sup> wrote that there is "no flat rule for successful results . . . individualizing the therapy is the key-note to successful therapy." It is my own opinion that the high percentage of failures reported by some authors is due in part to the lack of individualization of treatment, rather than a lack of potency on the part of the hormone preparation they were using.

During these years of investigation, equine gonadotropic hormones have been administered from the eighth to the eleventh day of the ovarian month. For a time, material which permitted a daily dose of 2,000 international units was made for me. It seems that the results with this material were far better than when I had to use 200, 400, or 500 I.U. as a daily dose. However, I am still uncertain as to how much better a 2,000 I.U. dose is than a 500 I.U. dose. Particularly during the war, the increase in environmental and emotional tension of our people has made it difficult to evaluate this particular point. We never give this material for longer than four ovarian cycles.

Hypo-ovarian function, whether primary or secondary, requires the same general sort of treatment: a preliminary preparation including both the improvement of the general health of the patient and the estrogen-progesterone ratio followed by three or four doses of equine gonadotropic hormone per month. Obviously, in primary hypo-ovarianism, the preliminary stages of treatment require more time than in secondary.

Dysmenorrhea, when associated with uterine hypoplasia, is not successfully controlled until increased uterine growth and improved function of ovaries and endometrium has been accomplished by preliminary "priming." When this has been achieved, equine gonadotropic hormone is used to prevent recurrence.

Menometrorrhagia is controlled by the use of prolactin until the amount of menstrual bleeding is normal.<sup>5</sup> The equine gonadotropic hormone is used to re-establish normal cyclic bleeding.

Some fibromyomatous growths are possibly the result of an unbalanced sex hormone chemistry due to pituitary-ovarian dysfunction. The surgical removal of the new growths usually fails to correct the fundamental underlying cause. Therefore, these patients have been treated with prolactin followed by equine gonadotropin (where indicated) in an attempt to correct part of the underlying causes of the new growth development. If normal menstrual periods are



# CONTROL OF MENSTRUAL DISTURBANCES AND HYPO-OVARIAN STERILITY

## Nine Years of Experience With Equine Gonadotropin

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**B**ECAUSE efforts to develop an infallible method of improving pituitary-ovarian function have so far eluded investigators, it does not necessarily follow that there are not presently available methods by the use of which at least a large portion of those suffering from faulty pituitary-ovarian function can be benefited, or cured. Therefore, this paper is presented, not as a final solution of the problem, but rather as an interim report on results which have been obtained with the use of equine gonadotropic therapy following satisfactory preliminary preparation with estrogens and progesterone.<sup>1</sup>

There are so many environmental, personal, and physiologic factors involved in each case that the statistics obtained from the study of 2,000 cases are probably no more valuable than the traditional Mark Twain comments would indicate. The statistics herein presented are not selected, and represent the uninterrupted flow of patients through my office during the last nine years. This report refers only to the patients who received equine gonadotropin, and does not include any others.

Clinical findings have shown that it is impossible to place patients into one of half a dozen pigeonholes, each one to be treated as a carbon copy of hundreds of others complaining of similar symptoms. We have attempted to treat each patient as an individual, trying to return all physiologic functions to normal before specific therapy is administered. It may well be that a portion of our good results are due to the improvement of their general physical well-being rather than entirely due to our plan of substitution therapy followed by equine gonadotropic hormones.

The first step, therefore, in our plan of treatment consists of a case evaluation of all of the patient's physiologic systems with treatment where indicated, whether these appear to have a direct bearing on her female reproductive system or not.

Following this, and at times coincidental with this form of attack, an effort is made to supply each patient with estrogen and progesterone, or antiestrogenic materials necessary to correct the symptomatic "complaints." In spite of numerous authoritative findings that estrogens are antigonadotropic, we are of the opinion that the carefully planned use of estrogens and progesterone (adjusted to meet each individual patient's personal requirements) not only has no harmful effect on the pituitary function, but instead, is advantageous to the degree that many of our results seem to be due, in part, to the "preliminary preparation." We have used the vaginal smear<sup>2, 3</sup>

Acknowledgments are made to the following companies for the use of their products: (1) equine gonadotropin supplied by Cutter Laboratories; (2) sterols supplied by Schering Corporation; (3) prolactin supplied by Armour Laboratories.

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re-established, equine gonadotropin assists in stimulating a more normal pituitary-ovarian relationship, with a consequent gradual reduction in the size of the tumors.

The treatment of hypo-ovarian sterility has followed the same plan as outlined above, and included all required tests of both husband and wife. During the nine-year period covered by this study, 301 women were treated for hypo-ovarian sterility with equine gonadotropin. One hundred fifty-eight pregnancies followed the treatment, 17 of which ended in abortions or miscarriages. There was one maternal death due to postpartum hemorrhage, and one infant died at the age of 22 days due to pemphigus.

Contrary to the reports from many sections of the country, hypothyroidism does not seem to be a frequent, important factor in our community.

In this series, excessive uterine bleeding and secondary amenorrhea seem to be correctable in a higher percentage than do the other disturbances listed. Menometrorrhagia patients respond to prolactin therapy, and when this is followed by equine gonadotropic hormones (where indicated) most of the patients maintain normal function without further treatment.

If all ovaries are recognized as potentially capable of manufacturing the proper quantities of the ovarian chemicals necessary for the maintenance of normal menstrual cycles; and if these chemicals were, first, supplied in the required physiologic amounts during a period of deficiency, and second, followed by a satisfactory method of stimulation of the ovaries, causing them to function normally without further treatment, then we would have a fundamental plan of successful therapy.

The efficiency of any method of ovarian stimulation is dependent, not only on the potency of the materials or modality used, but also on the condition of the patient as a whole and on the receptivity of her ovaries. With this plan, used in a series of selected cases over a period of nine years, better results seem to have been obtained with equine gonadotropin than with any other material used for ovarian stimulation.

TABLE I.

	CASES	PRELIMINARY THERAPY	NOT CURED		CURED	
			NO.	PER CENT	NO.	PER CENT
Amenorrhea primary	37	*	30	83.8	7	16.2
Amenorrhea secondary	81	*	24	17.3	67	82.7
Dysmenorrhea	357	*	92	25.8	265	74.2
Hypomenorrhea and oligomenorrhea	952	*	428	45.0	524	55.0
Menometrorrhagia	473	Anti-estrogenic material†	81	17.1	392	82.9
Anovulatory sterility	301	*	143	47.6	158	52.4
Total Patients: 1937	2201					

\*Estrogen-progesterone ratio.

†Prolactin, testosterone, progesterone, acetosy-pregnenolone.

hydroxyl groups. This process is known as demethylation, a prolonged and difficult reaction, in vitro as well as in vivo. Slow absorption from the oil solution and prolonged demethylation were considered the rationale for the use and study of dimethoxy stilbestrol. That this hope was justified is borne out by the preliminary report and by the present study. It is my opinion that estrogenic therapy has now reached a new peak, in that frequent dosage is no longer necessary for prolonged and effective therapeutic results.

Since publication of the preliminary report, the author has modified the dosage and composition of the product used. The previously recommended dose of 90 mg. (weekly injections of 30 mg.) gave adequate relief for a long period of time. However, there was a lag for a week before relief of symptoms became manifest. It was decided, therefore, to add 0.5 mg. of stilbestrol to each dose. Furthermore, the original dose was arbitrary; repeated trials proved that adequate relief could be obtained with a dose of 15 mg. per week for three weeks, a total of 45 mg. instead of the 90 mg. originally advocated.

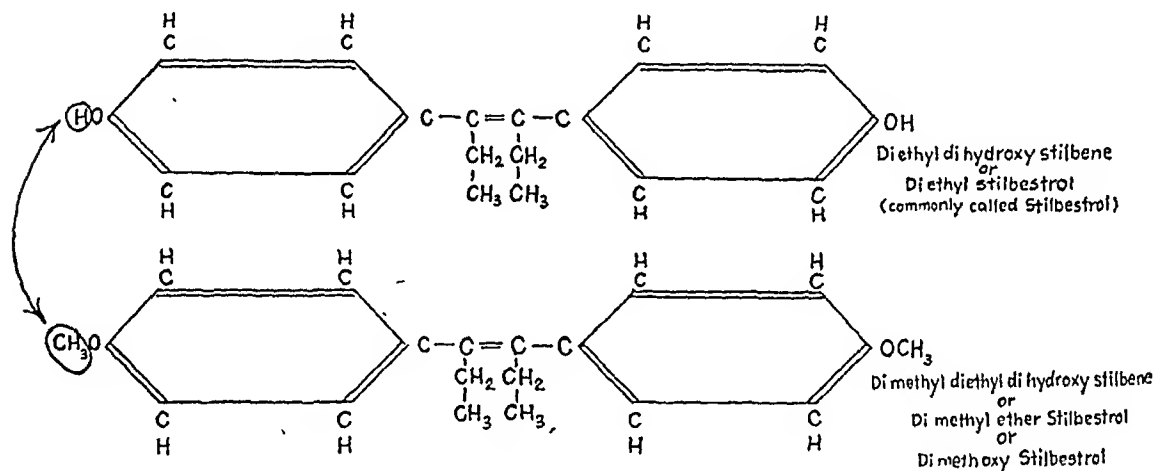


Fig. 1

Therefore, our present method of therapy consists of weekly injections of 15 mg. of dimethoxy stilbestrol in combination with 1.0 mg. of stilbestrol, in oil, for three weeks. The degree of well-being experienced by the patients was dramatically out of proportion to the small amount of stilbestrol added. The only explanation that can be offered for this phenomenon is a synergistic action between the stilbestrol and the dimethoxy stilbestrol, which was greater than the simple additive effects expected.

During the past two years, 56 new cases have been observed, all from private practice. As in the original group of 49 cases previously reported, there was complete relief from all symptoms of menopause. There were no toxic reactions of any kind. This therapy was not supplemented with any other medication. The average number of symptom-free days were equal (144 days) with this new dosage, to those of the former group with the previously larger dose. The mixing of related synthetic estrogens has never been attempted before in the treatment of menopause, although this investigator is using a similar preparation of different proportion in the suppression of lacta-

## MIXED SYNTHETIC ESTROGENS—THEIR USE IN THE MENOPAUSE

### (Dimethoxy Stilbestrol and Diethylstilbestrol)

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ENDOCRINE therapists have attempted to attain new methods for the administration of hormones. In place of the frequently repeated dosage, the modern trend is to administer larger doses of slowly absorbable materials, with a view toward prolonged action. Protamin-insulin and adrenalin in oil are examples of the expression and intent of the newer hormone therapy. In the field of sex hormones, little or no progress has been made in this direction. Esterification of the steroids, pellet implantation, the development of a large number of synthetic estrogens (other than the steroids), estrone in aqueous suspension, and stilbestrol in aqueous suspension have failed to overcome the disadvantages of frequent dosage. The shortcomings of pellet implantation are too well known to bear repetition; esterification of the steroid estrogens, as well as the application of the entire list mentioned, has not appreciably cut down the need for frequent medication.

Of all the synthetic estromimetic agents, diethylstilbestrol, commonly known as stilbestrol, is pre-eminent. There is little doubt of its therapeutic efficacy and estrogenic potency. However, its toxic side reactions and the transitory character of its effect have considerably lessened its usefulness. Attempts to overcome these defects by chemical modification have proved unsatisfactory. Published results of the estrogenic effects of other more recent synthetic estromimetic agents indicate these to be less effective than stilbestrol. Their therapeutic efficacy, at the same dosage level, is far below that of stilbestrol; with an increased dose, necessary to obtain comparable therapeutic effects, toxic symptoms of equal or greater severity appear.

Four years ago the author began a clinical investigation of all stilbestrol derivatives for potency, toxicity, and duration of activity, with the ultimate object of determining the most efficient estrogenic agent. This proved to be dimethoxy stilbestrol (dimethoxy diethyl stilbestrol), dissolved in oil for intramuscular injection. A preliminary report,<sup>1</sup> published in 1944, cited the results obtained in the treatment of the menopause and in the suppression of lactation. Further results are herewith reported with this stilbestrol derivative in the menopause.

For a clearer understanding of the pharmacology of dimethoxy stilbestrol the structural formulae are shown in Fig. 1. The difference is the presence of the methyl ( $\text{CH}_3$ ) radicals in place of the hydrogen (H) atoms in both of the hydroxyl (OH) groups of the dimethoxy stilbestrol.

In the body, before any therapeutic action can take place, stilbestrol must be formed from this derivative. Referring to Fig. 1 again, the obvious process is that of substituting the hydrogen atoms for the methyl radicals to form the

# SURGERY IN THE UTERINE FIBROID, A PLEA FOR MYOMECTOMY

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THE uterine fibroid or myoma uteri, a benign organoid, solid neoplasm, has its origin in the fibromuscular component of the uterus as a local hyperplasia. By condensation of the surrounding fibromuscular structure and the peculiarity of its intrinsic growth, a capsule is developed through which the tumor receives its nourishment and from which, usually, it can be enucleated. Interference with its rather scant arterial supply is responsible for hyaline, necrobiotic, or necrotic degeneration; while edema, liquefaction necrosis, or cystic formation results from interference with its relatively larger venous and the lymphatic return.

The etiology, not unlike that of other new growths, is unsettled. However, the endocrine theory of excessive and persistent estrogenic stimulation in the absence of pregnancy, without adequate luteinizing influence, appears at least plausible, if not rational.

The great majority of uterine fibroids is encountered clinically from the thirtieth to the fiftieth year. Fifty to 75 per cent of all women 35 years of age and over who come to necropsy have fibroids. The American Negro woman is said to be affected three to one to the Caucasian; while in the full-blooded African, the fibroid is almost a nonentity. Finally, women who have not borne children are said to have a higher incidence of fibroids.

Growth of the tumor generally is slow, due to the paucity of arterial blood; however, the growth may be accentuated by menstruation and pregnancy; is inversely proportional to the amount of fibrous tissue and the age of the woman, and ceases, usually, after the menopause.

As to location, the fibroid is intramural, subserous, submucous, intraligamentous, or parasitic. It should be remembered that only the intramural and the submucous varieties cause abnormal uterine bleeding, either menorrhagia (too much menstrual blood or too long menstrual flow) or metrostaxis (bleeding from the uterus other than menstrual), respectively, or both. The intramural produces menorrhagia by either an increase in the endometrial area by the large fibroid(s) resulting in excessive amount of menstrual blood, or atony of the uterine muscle from multiple small fibroids with prolongation of the menstrual flow. On the other hand, the submucous fibroid produces, characteristically, metrostaxis by superficial necrosis.

Regarding treatment, the mere presence of an uterine fibroid should be no indication for surgical intervention. Rather, there should be incontrovertible reasons, such as hemorrhage, not otherwise controllable, pain, pressure symptoms, rapid growth, signs of tumor degeneration, interference with the pregnant states, cosmetic, and marital purposes. The therapy of the uterine

tion. Further investigation is being conducted, at this time, to determine chemically the excretion products of stilbestrol. This will enable the exact calculation of the time the drugs are in the circulation and the duration of their effects after complete elimination.

Bleeding occurred in six cases. In three of these the bleeding was scant, did not recur, and required no further treatment. These cases were regarded as due to withdrawal. The other three cases occurred in patients previously curetted and irradiated for hyperplasia of the endometrium. Secondary curettage revealed a recurrence of the hyperplasia as the cause of the bleeding. Obviously, the use of this or any other estrogen is ill advised in the treatment of menopause following radiation.

The results obtained in the 105 cases, studied during the last four years, convince this investigator that the combination used is the most desirable estromimetic agent, and approaches the ideal therapeutic means for the treatment of menopause. The slow absorption and metabolism of the drug makes for the realization of the desired effects of less frequent dosage, prolonged action, and absence of toxic symptoms.

### Summary

The effects of mixed synthetic estrogens\* was studied for the past four years in a group of 105 cases of menopause.

The following results were obtained:

1. Freedom of symptoms for approximately four months.
2. No toxic reactions.
3. Three cases of withdrawal bleeding.
4. Synergistic action between the dimethoxy stilbestrol and stilbestrol.

The author wishes to express his thanks to Dr. A. Koplowitz of Brooklyn for his co-operation and his use of the mixed estrogens on his private cases.

To the Forbes Laboratories of Elgin, Illinois, my thanks for their co-operation and preparation of the mixed estrogens which made this study possible.

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\*The following formula is the one used:

Dimethoxy stilbestrol	_____7.5 mg.	} in 1 c.c. of sesame oil
Stilbestrol	_____0.5 mg.	
Chlorobutanol	_____0.5 mg.	

tive, operative, and postoperative preparation, technique, and care of the patient, respectively. In 1,500 consecutive fibroids for which surgery was employed, 900 were treated by myomectomy and, of these, 92 were of the submucous type. The varieties in this latter group ranged all the way from the simple sessile to the pedunculated having attachment to the upper lateral uterine wall, resulting in partial inversion of the uterus and fundal attachment, with marked distension of the vaginal canal by the polyp. There was no mortality or other worth-while complication following myomectomy in this series of submucous fibroids.

### Procedure

The following is our routine of procedures: A physical examination is made for possible focus of infection in the teeth, tonsils, sinuses, endocervix, adnexae, or blood and, if found, it is vigorously treated. If the red blood count is below 3,500,000, small therapeutic blood transfusions (200 c.c.) are given daily until the count is well above the 3.5 count; if the red count is 3.5 millions, one prophylactic transfusion of 500 c.c. is given; if the bleeding time is prolonged beyond normal, vitamin K is given until normal is obtained; if the white cell count is below 6,000, 10 c.c. of sterilized milk is administered intragluteally daily for two days; the count is generally raised from 50 per cent to 100 per cent or more thereby; if the blood sedimentation rate (Cutler) is 24 mm. or above for the hour, it is critically evaluated before operation.

Rarely, a patient comes in with uterine bleeding and with a very low red cell count. Formerly, we stopped the bleeding by packing the uterus and vagina with antiseptic gauze; recently, we have been injecting 25 mg. of stilbestrol in oil into the anterior lip of the cervix uteri with control of the bleeding within one to six hours and until the blood picture is built up sufficiently for operation. It is unusual to make more than two such injections. The blood pressure, heart, lungs, and urine are checked to determine the choice of anesthetic.

On the day preceding operation, the vagina is prepared as for cesarean section with a solution (1 to 250) of neutral acriflavine or zephiran solution (1 to 1,000) on gauze left in overnight; the patient is given, by hypodermoclysis, 1,000 or 1,500 c.c. of 5 per cent glucose in normal saline solution the night before and the same repeated on the morning of operation.

After entering the abdominal cavity, myomectomy, even multiple (we have removed as many as 23 fibroids from an uterus), is done, unless the uterus is so distorted, very rarely by the tumors, that its contour is unidentifiable, or the endometrium is extricated almost entirely in removing the fibroids, or there is coexistent adnexal disease; in either event, hysterectomy becomes the procedure of choice. During multiple myomectomy, as each tumor is enucleated its cavity is sewed up from bottom to top with a continuous suture of 0 chromic catgut, and the line of incision is peritonealized with an inversion continuous suture of 00 plain catgut. And if, in the judgment of the operator, the incisions in the uterus have been too numerous and/or too extensive to safely permit pregnancy, the tubes may be crushed, transfixed, and doubly ligated, preferably with linen or cotton suture, thereby precluding only possible reproduction while, at the same time, preserving menstruation with all of its connotations. The ligated tubes with their mesosalpinges have been used, not infrequently, to peritonealize the incisions in the uterus further minimizing the possibility of adhesions.



fibroid has run a gamut with varying success and obvious disappointment from ergot to irradiation (deep x-ray and radium) including bilateral oophorectomy, electrolysis, and surgery—hysterectomy and myomectomy.

It is with this latter method (surgery), especially myomectomy, even multiple, particularly for the submucous variety during the childbearing period, that this report is chiefly concerned.

Ever since the first celiotomies for uterine fibroids by Heath and Clay of Manchester, England, in 1843 to 1844 and Burnham, an American, in 1853, abdominal hysterectomy has been the prevalent procedure of choice for uterine fibroids. True, there have been sporadic myomectomies for the subserous, rarely the interstitial, and rarer still for the submucous. But as sepsis, sapremia, and death followed the latter procedure in such alarming proportions, the physician purposely and with justification shied away from further attempts at myomectomy, even for the interstitial, and most times the subserous variety. Consequently, myomectomy for practical purposes had become well-nigh a lost art.

After observing for a long time and not satisfied with the decimating and otherwise unpredictable results following hysterectomy for uterine fibroids whereby the woman was suddenly deprived of menstruation, possible reproduction, endocrine balance within thirty months, and domestic tranquility, we undertook a critical study with the view both to overcoming the objections of the opponents of myomectomy, such as hemorrhage, adhesions, infections, and tumor recurrence, and to recasting an improved technique for myomectomy incompatible with the above drawbacks and shortcomings of hysterectomy, and free of the heretofore disappointments and disasters of myomectomy.

Pursuant thereto, all cases with fibroids having abnormal uterine bleeding received a diagnostic endometrial curettage before decision for surgical intervention in order to ascertain whether or not there was a coexistent hyperplasia endometrii, which, alone, could account for the bleeding. If the curettings were positive for hyperplasia of the endometrium, the patient was given, primarily, the benefit of organotherapy such as thyroid extract, progesterone, pregnant mare's serum, or testosterone propionate which usually regulated or controlled such bleedings. These failing, and with the diagnosis negative for hyperplasia, cause for the bleeding was assigned to the presence of submucous fibroid(s) or extensive adenomyosis interna; in either event, surgery was the indicated procedure. In no case was unsuspected carcinoma of the endometrium encountered.

Extensive adenomyosis interna by enlarging the uterus and increasing the endometrial area would produce menorrhagia; but the inability to enucleate the mass from the uterine muscle by its lack of encapsulation offers ready differentiation; also, its softer texture and darker gray color, together with incising the mass and finding chocolate-colored blood, complete clinically the differential diagnosis from an intramural fibroid.

The successful surgical treatment of fibroids, in addition to that mentioned above for uterine bleeding consisted, in our procedures, of routine preopera-

## Conclusions

The failures and disappointments which followed the former over-all technique of myomectomy for the intramural, but more especially for the submucous fibroids, may be accounted for by (1) failure on the part of the operator both to appreciate that, in the submucous type, the involved endometrium is infected particularly about the base of the pedunculated, and in the necrotic areas of the sessile variety, and to do something about it; (2) lack of the preoperative, operative, and postoperative use of the sulfonamide drugs and recently penicillin as outlined above to prevent or control infection; (3) failure to eradicate a chronic infective endocervicitis or other detectable focus of infection prior to operation; (4) failure to prepare the vagina as for a cesarean section; (5) failure to provide postoperative drainage of the uterine cavity following the submucous operations; (6) failure to institute the proper measure(s) to prevent or minimize passive congestion of the uterus following myomectomy operations.

## Summary

1. The uterine fibroid is a benign neoplasm, and its mere presence should be no cause for surgery.

2. Only incontrovertible reasons, such as hemorrhage, pain, pressure symptoms, signs of tumor degeneration, rapid growth, interference with the pregnant states, cosmetic, and marital purposes should indicate surgical intervention.

3. Myomectomy, even multiple, whereby endocrine balance, menstruation, and reproductive possibility are preserved, should be preferable to hysterectomy.

4. The preoperative, operative, and postoperative preparation, technique, and care, respectively, as herein outlined, have enabled us to perform successfully 900 consecutive myomectomies for the interstitial and submucous types of fibroids with complete control and/or prevention of infection.

5. The objections by opponents of myomectomy such as hemorrhage, infection, adhesions, and tumor recurrence have been effectively overcome in our procedures.

6. This paper is presented with the hope that the widespread use of myomectomy, as described, will merit its recognition as the procedure of choice in the surgical treatment of uterine fibroids.

As a prophylaxis against the possible early recurrence of fibroids, the myomectomy incision preferably on the anterior uterine wall or the posterior is carried down through the endometrium sufficiently long to admit two fingers into the uterine cavity, and with the thumb on the outside and two fingers within the uterine cavity, the entire muscular wall of the uterus is palpated carefully and, if a very small interstitial fibroid(s) is detected, it is enucleated. A fibroid so small as to escape detection by such palpation, in our experience, will not likely develop or cause trouble under seven to ten years. And since the great majority of fibroids is encountered clinically in the fourth and fifth decades, the end of that seven- to ten-year period might well carry the woman into the menopause, when fibroids rarely develop or grow further. That such preservation of menstruation and reproductive possibility, two characteristics to which every woman is entitled, physiologically and biologically as an end fully justifying the means here, is incontrovertible.

We do not elect to do surgery (hysterectomy or myomectomy) for uterine fibroid in the presence of fever, leucocytosis, or rapid sedimentation rate. However, if the case must be operated on, 60 grains of sulfadiazine and, recently, 300,000 units of penicillin are given the patient on the day before operation, and at least 300,000 units of penicillin given on the day of and three days following operation to control the infection; also 5 Gm. of sulfathiazole and sulfanilamide crystals are sprinkled on and about the operative field before closing the abdomen to prevent infection.

Furthermore, since all submucous fibroids have infection of the endometrium as an invariable accompaniment, particularly about the base of the pedunculated and in the necrotic areas of the sessile types, we use the sulfonamides and penicillin preoperatively, during operation and postoperatively, as outlined above, to control and prevent infection.

In operating for the submucous pedunculated fibroid, a longitudinal incision is carried through the anterior uterine wall sufficiently to allow full access to the uterine cavity. After exploring the uterine walls for small interstitial fibroids as described above, an endometrial cuff is made around the base of the pedicle, the pedicle is resected from the muscular wall, hemostasis is effected with 0 chromic catgut, and the wound is covered with the cuff, using 00 plain catgut. In case of the submucous sessile fibroid, the endometrium over the tumor is divided with a longitudinal incision and dissected from the tumor, the tumor is enucleated from its bed, the cavity is obliterated the same as in the interstitial and the area covered with endometrial flaps using 00 plain catgut. Before closing the uterus after freely sprinkling the sulfonamide granules in its cavity, the cervical canal is dilated with Hegar's dilators from the uterine cavity, if not already done so by a submucous polyp, in order to insure adequate postoperative uterine drainage. Moreover, passive congestion is both conducive to infection and inimical to tissue healing. A retroverted uterus favors passive uterine congestion; and the postoperative bed period not unlike the postnatal bed period predisposes to passive congestion of the uterus, the uterine veins being devoid of valves. So, in order to obviate such a menace to the myomectomy, a retroversion is corrected by one of the ligament suspension operations, and the head of the bed is elevated at least 18 inches for five or six days following operation.

There is no doubt, from the above prerequisites, that myomectomy may be more technical and time consuming than supravaginal hysterectomy, but the preservation of the genital functions, the promotion of nervous and mental stability and tranquility, and the maintenance of wholesome family relations outweigh by far, in our considered opinion, any adverse consideration of time or incidental operative technique.

as possible, and treated energetically and not casually. To do this we must know how great is the extent of hemorrhage. Rough estimates of the amount of blood lost are unreliable and, for over five years, the author has used a simple method which is easy of operation and accurate.

It consists of a sterile metal plate which is slipped beneath the patient's buttocks after the birth of the baby. This plate drains into a glass jar, of over one liter capacity, supported by a ring bracket attached to the delivery table. The amount of blood is at all times visible to the obstetrician and, if he is wise, he will plan his campaign of treatment to control the bleeding and replace the loss when the amount passes 300 c.c. Signs of hemorrhage, such as a rising pulse, lowered blood pressure, and pallor, do not appear immediately, and it is much better to start the administration of plasma to be followed by transfusion if necessary when the amount of hemorrhage is known rather than to wait for the clinical evidences previously mentioned.

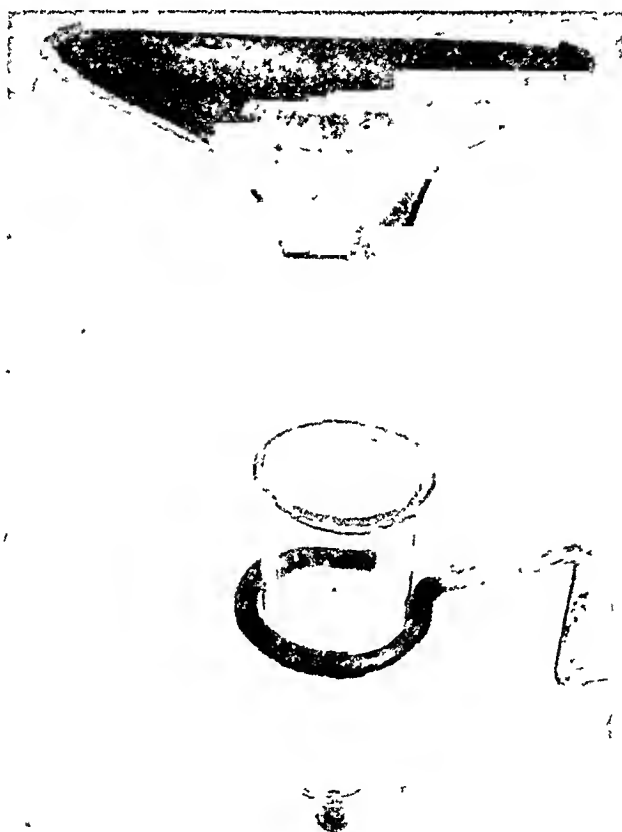


Fig. 1.

In 1942 Davis and Boynton<sup>1</sup> of the Chicago Lying-in Hospital described a new technique for the management of the third stage of labor. The technique consists in the intravenous injection of 1/320 grain of ergotrate (ergonovine) immediately after the birth of the child's head, a pause of half a minute to a minute before delivering the shoulders and the body. The effect is twofold. First, it shortens the third stage of labor, and second, and more important, it lessens the blood loss. Any method which brings this about is worth while, provided its employment is not accompanied by any drawbacks. By employing the method of measuring blood loss described previously it is possible to compare

## THIRD STAGE OF LABOR

### I. Measurement of Blood Loss

### II. Intravenous Ergotrate

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THAT time elapsing from the birth of the child until the extrusion of the placenta, or third stage of labor is probably the worst managed in the conduct of delivery. It is at the same time fraught with more danger to the mother than the first two stages, for it is at this time that hemorrhage occurs, and not only blood loss may threaten life, but measures to combat it may introduce infection to a woman made susceptible by the bleeding.

It is necessary to unlearn almost as much as we learn in medicine; progress often requires the discard of firmly rooted ideas. The third stage of labor is no exception. The first to forget is the teaching that the length of the third stage is from fifteen to thirty minutes—simple observation will prove it to be much shorter than this, separation often occurring within a minute or two after the birth of the baby. The second to forget is that the attendant should wait at least thirty minutes before attempting to expel or express the placenta. Time is no factor in this determination. The third stage is divided into two parts: the separation of the placenta from the uterine wall, and then its expulsion. Once the placenta is separated, it should be expressed. Spontaneous expulsion of the placenta today is not often seen, the use of analgesia and anesthesia prevents this. Expulsion of the placenta after its separation minimizes hemorrhage.

What is the physiologic or normal blood loss? This is somewhat dependent upon the size and weight of the individual. The average amount measured by four authorities is 348 c.c.

#### AVERAGE LOSS OF BLOOD AT DELIVERY

Williams	244 c.c. measured
Ahlfeld	505 c.c. measured
Tucker	300 c.c. measured
Pastore	244 c.c. measured

This loss is compensated for by the increased blood volume built up during pregnancy; this is about 500 c.c. The blood constitutes 5.3 per cent of the body weight before conception and increases to 8.4 per cent at the end of pregnancy, so the loss of this amount or one pint is usually without symptoms. Any amount above 500 c.c. is considered as pathologic or a postpartum hemorrhage. Blood loss is important not only because of its immediate effects such as profound anemia and even death, but, as stated above, it predisposes to infection.

We all agree that hemorrhage in the parturient is important. Blood is a precious fluid and should be conserved; its loss should be prevented as far

TABLE III. LENGTH OF THE THIRD STAGE

<i>After second stage, ergotrate i.v.</i>	6.0 minutes*
Excluding 6 cases of retained placenta, with an average third stage of 2 hrs., 50 minutes, the average duration in 424 cases was	4.0 minutes
Controls	9.88 minutes

\*259, or 60 per cent, had a third stage of 4 minutes or less.

Are there objections to this method? Late puerperal bleeding and an increase in the incidence or intensity of "after pains" were no more common after this technique than before its employment. Retention of the placenta occurred six times, and in two of these it was due to error in technique, the extraction of the baby's body followed too soon after the injection of ergotrate. This leaves four cases in 430, which is the incidence of retention in all cases (about 1 per cent). It is not used in breech deliveries and in any case of vertex delivery where the body is large and much difficulty is anticipated in delivery of the shoulders.

### Conclusions

1. Blood loss at delivery should not be estimated but measured.
2. Measurement of blood loss can be easily done by a simple apparatus.
3. Separation of the placenta occurs almost immediately after the birth of the child; this is accomplished by uterine contraction.
4. Spontaneous expulsion of the placenta is uncommon after the use of analgesia and anesthesia. The placenta should be expressed after its separation; nothing is gained by delay.
5. Ergotrate given intravenously after the birth of the head shortens the third stage and minimizes the blood loss.

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26 SOUTH GOODMAN STREET

the length of the third stage and the blood loss in cases where the Davis method was used with a number of controls where the older technique of the third stage was employed.

The modern conception of the mechanism of the separation of the placenta is that it is not due to the formation of a retroplacental clot which pushes off the placenta, but that it is due to uterine contraction. The uterus as it contracts becomes smaller at the placental site; the placenta does not change in size or bulk, so there is a cleaving away from its attachments to the uterus. The more rapidly this occurs, the smaller will be the ensuing hemorrhage, hence the arguments for this method. The more protracted the third stage, the greater the bleeding.

Timing is an important element in the success of this method. Some time before delivery is imminent, the ergotrate is prepared in the needle. The anesthetist, or whoever is to give it, familiarizes himself with the cubital space in the patient's arm, and a tourniquet is placed loosely about the arm. As the head emerges over the perineum the injection is rapidly made. Before the delivery of the shoulders there is a pause of a minute during which time mucus may be cleared from the pharynx of the baby. This pause of one minute gives time for the separation of the placenta while the cervix is held open by the body of the baby; if the delivery is completed too rapidly, the cervix will close down and placental retention results.

Results from the employment of this technique in 430 private cases are shown in Tables I and II.

TABLE I. AVERAGE MEASURED BLOOD LOSS

<i>No ergotrate until after birth of baby</i>		
75 cases (controls)		327 c.c.
<i>After ergotrate i.v. in second stage</i>		
430 cases		181 c.c.
46 cases of these where blood loss was chiefly from lacerations or episitomies		554 c.c.
384 cases where blood loss was almost entirely uterine		136 c.c.

TABLE II. AMOUNT OF BLOOD LOSS—430 CASES

10 to 100 c.c.*	215 or 50	per cent
101 to 200 c.c.	94 or 22	per cent
201 to 300 c.c.	47 or 11	per cent
301 to 400 c.c.	28 or 6.5	per cent
401 to 500 c.c.	18 or 4	per cent
500 c.c. and over†	28 or 6.5	per cent

\*116 of these lost less than 50 c.c.

†This group were cases of loss chiefly from lacerations or episiotomies.

Inasmuch as this is a consideration of blood loss as affected by uterine separation and expulsion, it is obvious that loss from laceration of the vagina or perineum should be excluded; this was done in 46 of the 430 cases, leaving 384 deliveries where ergotrate was given intravenously after the birth of the head, and the average loss was 136 c.c., almost entirely from the uterus.

expected date of delivery (day 21 or 22) to determine the number of fetuses or placentas remaining.

In the control Group A, three rats were anesthetized with ether and the skin was pinched with a hemostat. In two animals, attempts to kill the fetuses by rupture of the amniotic sacs were unsuccessful, living fetuses being subsequently born. In Group B, those portions of the uterus containing a fetus and placenta were removed. In Group C, the fetuses were killed in three animals by rupturing the amniotic sacs by external compression under anesthesia, in one animal by stabbing each fetus through the uterine wall, in another by severing the cervical spines through the uterine wall, and in the last animal by withdrawing each umbilical cord with a crochet hook and severing it.

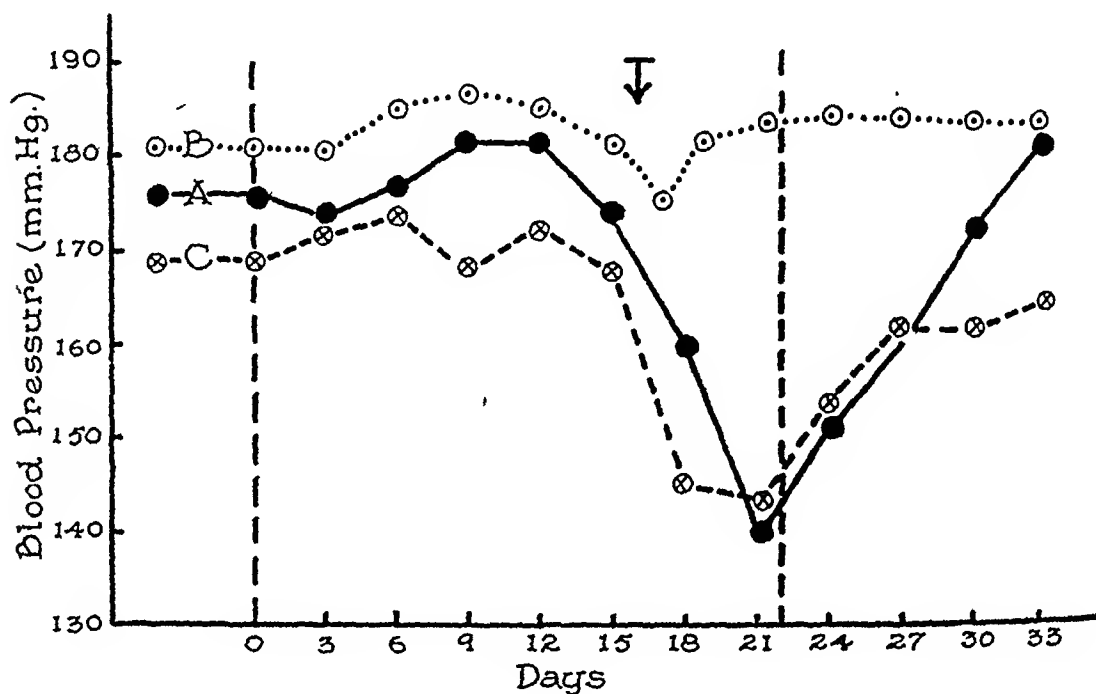


Fig. 1.—The blood pressure during pregnancy in three groups of hypertensive rats.

Ordinate: Mean systolic blood pressure for each three-day period (in mm. Hg.)

Abscissa: Days, beginning from the time of conception. The arrow marks the time that a control operation was performed (curve A), or hysterectomy (curve B), or removal of the fetuses alone (curve C).

## Results

*Group A.*—The systolic blood pressures of the five rats in this group had stabilized at levels between 150 and 210 mm. during the week before conception, the average for the group being 176 mm. In three animals there was a rise of pressure during the first twelve days, and, in all, the blood pressure began to fall between day 12 and day 15, reaching the lowest point at the time of delivery and returning to its original level about ten days post partum. The mean blood pressure for the group for each three-day period after conception is illustrated in Fig. 1, curve A.

*Group B.*—The six rats in this group began pregnancy with blood pressures of 155 to 205 (mean = 181). Hysterectomy was done on five of these just after the blood pressure had started to decline. There was a sharp, transient drop of systolic pressure on the day following operation and this was attributed to the more extensive operative procedure. Within forty-eight hours the blood pressure of each animal had returned to its previous level and showed no further change (curve B). The sixth animal aborted both the placentas and the fetuses on day 16, the day after an attempt had been made to remove the fetuses and leave the



## RELATION OF THE FETUS AND PLACENTA TO THE DECLINE OF HYPERTENSION IN PREGNANT RATS\*

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PRECEDING papers<sup>1, 2</sup> have shown that there is a marked fall of blood pressure in hypertensive rats during pregnancy, that a similar though slight decline occurs in normal pregnant rats, and that endocrine factors alone do not appear to be responsible for this phenomenon. The fall of blood pressure in hypertensive dogs or rats during late pregnancy has been attributed to the antipressor or compensatory action of fetal kidneys,<sup>3, 4</sup> while others<sup>2, 5, 6</sup> have attributed the effect to either the circulatory or endocrine alterations associated with the placenta.

The purpose of this study was to determine whether it is the fetus or the placenta which causes this fall of blood pressure. Three groups of hypertensive rats were studied during the course of pregnancy. The first, a control group, received a "dummy" operation on the fifteenth or sixteenth day of pregnancy; the second group had a hysterectomy at the same period; and in the third group the fetuses were killed and the placentas were allowed to remain in situ.

It has been well established that the placenta continues to function as an endocrine gland after the death or removal of the fetus. In most species, the pregnancy continues to term and the placentas are then delivered. This has been demonstrated in rabbits,<sup>7</sup> mice,<sup>8</sup> rats,<sup>9-11</sup> and monkeys.<sup>12</sup> Huggett and Pritchard<sup>11</sup> state that no matter how fetal death is produced in rats the placentas survive, grow, and differentiate histologically in comparatively normal fashion, especially if the allantoic mesodermal component is present—that is, eleven days after conception. From their studies of pregnancy after removal of the fetus in monkeys, Van Wagenen and Newton<sup>12</sup> conclude that "during the time of placental retention, the animal remains physiologically pregnant" with respect to continued weight gain and edema, appearance and pigmentation, persistence of ureteral dilatation, high excretion of estrogens and androgens, and with respect to the time of onset of labor and initiation of lactation. In our third experimental group, therefore, we have assumed that the placenta continued to function after fetal death so long as its presence could be demonstrated by daily palpation.

### Methods

The methods of initiating hypertension and following the blood pressure, and the criteria for the selection of animals for the experimental groups have been presented.<sup>2</sup> Pregnancy was dated from the appearance of the sperm plug, and operation was performed on the fifteenth, sixteenth, or seventeenth day following conception. Daily abdominal palpation was done until after the

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### Summary

The fall in blood pressure observed in rats during late pregnancy is abolished by hysterectomy or by complete abortion, but still occurs when the placentas survive experimental death of the fetuses. It is suggested that the mature placenta results in this decline of hypertension either by causing maternal circulatory changes mechanically or by contributing enzymatic antipressor substances.

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placentas in situ. It is included in this group, and the behavior of its blood pressure was identical with those in which the entire uterus was removed.

*Group C.*—During the week before conception, the systolic pressures of these six rats had stabilized at levels ranging from 140 to 200 mm., with a mean of 169 mm. for the group. The fetuses were killed at the time and in the manner indicated above. Following operation, daily palpation revealed that four of the rats emptied their uteri twenty, twenty-one, twenty-three, and twenty-six days after conception respectively, and bleeding from the vagina was noted at these times. In two animals there was no evidence of delivery, and the uterine swellings gradually decreased in size, suggesting complete reabsorption. In contrast to Group B, the blood pressure continued to decline in every animal, and then rose again four to ten days after surgery in all but one rat in which the hypertension never returned. The mean values for each three-day period are plotted in Curve C. The three curves are superimposed to show the similarity in the timing and magnitude of the blood pressure fall between this last group and the controls (Group A).

### Discussion

The fact that the decline of hypertension in late pregnancy is prevented by hysterectomy or by spontaneous abortion of both the fetuses and the placentas, but not by eliminating the fetuses alone, establishes the placenta as the essential etiologic factor in the rat. The mechanism by which the mature placenta accomplishes this is not clear. That it is due to its endocrine products seems unlikely in view of our failure to simulate the blood pressure fall by any of the hormones or combination of hormones tested.<sup>2</sup> The maternal circulatory adjustments incident to a low resistance arteriovenous shunt at the placental sites<sup>13</sup> remain as a possible explanation.

An additional explanation, not heretofore considered, is the enzymatic contribution of the placenta to the maternal blood. Pregnancy in both man and animals results in the appearance of new enzymes in the maternal plasma. Among these are the "*abwehrferments*" of Abderhalden;<sup>14</sup> histaminase;<sup>15</sup> and certain peptidases, such as those which destroy pitocin and pitressin.<sup>16</sup> In addition there is a marked increase in the ability of the plasma of pregnant human subjects to destroy angiotonin.<sup>17</sup> In each instance, the "protective" enzyme reaches its peak at the end of pregnancy, and if experimental renal hypertension is of humoral origin, then the placental contribution of enzymes capable of destroying pressor substances might be a factor in the decline of hypertension.

It has been shown that normal rabbits<sup>18</sup> and rats<sup>2</sup> have a decline of blood pressure in late pregnancy, and from this, Corbit argues that the production during pregnancy of a specific antipressor substance accounting for the fall of blood pressure in hypertensive rats cannot be postulated unless the pressor substance which it presumably neutralizes plays a role in the maintenance of normal arterial tension. We know now that the renal pressor system does operate in the maintenance of normal blood pressure (reviewed by Ogden<sup>19</sup>) and that the adrenal cortex is essential for the maintenance of both normotension and hypertension.<sup>20</sup> An antipressor substance produced in late pregnancy might, therefore, account for the drop in arterial tension in both normal and hypertensive animals.

TABLE I. EFFECT OF PREGNENINOLONE ON THE MENSTRUAL CYCLES OF ADOLESCENT GIRLS  
WITH LATE PERIODS

CASE NO.	AGE	AGE MEN-STRUA-TION BEGAN	MENSTRUAL CYCLE BEFORE TREATMENT IN DAYS	MENSTRUAL CYCLE DURING TREATMENT IN DAYS	MENSTRUAL CYCLE AFTER TREATMENT IN DAYS	NO. OF MONTHS TREATED	DAYS OF CYCLE TREATED	DAILY DOSE IN MG.
1	14	14	180	0	0	3	10 days each	5
2	13		0	0	0	1	all	5
3	16	12	25 to 49	28	60	3	14 to M*	5
4	16	13	35 to 60	28 to 35	34	4	18 to M	5
5	18	12	42 to 49	28 to 29	28 to 30	13	18 to M	10
6	15	16	25 to 60	23 to 25	33 to 38	17	18 to M	5
7	11	10	33 to 60	28 to 30	35 to 42	3	18 to M	5
8	15	14	73 to 91	26 to 35	28	15	18 to M	5
9	14	13	35	35	35	2	25 to M	5
10	16	13	90 to 270	0	660	3	10 days each	5
11	18	11	35 to 60	0	42 to 70	1	14 days	5
12	17	11	150 to 365	30 to 35	0	15	18 to M	15
13	15	12	33 to 60	33 to 34	30	3	10 days each	10
14	13	11	28 to 60	28	28	8	18 to M	5
15	17		0	0	0	1	10 days	5
16	19	10	21 to 40	26 to 29	28 to 60	5	18 to M	5
17	11	11	21 to 45	29 to 34	42	9	18 to M	5
18	13	12	450	0	0	2	all	5
19	15	11	35 to 50	28	35	13	18 to M	5
20	16	15	33 to ?	32	30 to 32	1	14 to M	5
21	16	14	27 to 35	28	28 to 30	4	18 to M	5
22	18	13	37 to 38	31	34 to 38	4	18 to M	5
23	17	13	700	0	0	2	all	5
24	18	13	120	24	30 to 60	5	18 to M	5
25	19	14	11 to 68	29 to 32	pregnant	16	18 to M	5
26	17		0	0	0	1	10 days	5
27	15	15	53	26 to 36	28	9	18 to M	5
28	17	16	50 to 60	28	120	4	18 to M	5
29	14	12	60	0	0	1	all	10
30	14	12	35	28	35	1	18 to M	5
31	15	13	35 to 175	26 to 28	42 to ?	3	18 to M	5
32	16	14	50	28	30 to 120	8	18 to M	5
33	17	15	60 to 90	28	60	18	18 to M	5
34	14	13	60	30	32	4	18 to M	5
35	14	13	70	14 to 32	35 to 90	11	18 to M	5
36	15	13	42 to 60	29	45	2	18 to M	5
37	17	15	90 to 120	0	120	5	all	5
38	17	12	21 to 35	28	120	6	18 to M	5
39	17	14	14 to 35	24 to 34	24 to 35	20	18 to M	10
40	14	13	42 to 56	30 to 37		10	18 to M	5
41	16		0	0	0	7	18 to M	5
42	17	13	21 to 35	26 to 30	28	9	18 to M	10
43	12	12	30 to 35	29 to 33	29 to 33	4	18 to M	5
44	14		0	0	0	3	10 days each	5
45	15	13	35 to 42	33 to 34	35	7	18 to M	5
46	14	13	60 to 90	64	60	19	18 to M	5

\*M—the day menstruation begins.

# EFFECT OF PREGNENINOLONE ON THE MENSTRUAL CYCLE OF ADOLESCENT GIRLS WITH OLIGOMENORRHEA\* OR AMENORRHEA

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IT IS worth while to attempt to find additional clinical uses for the potent, orally effective hormone, pregnenolone. This crystalline substance<sup>4, 5</sup> differs only slightly from progesterone in that there is substitution of OH for H in the 17-position and subtraction of H<sub>2</sub>O from the side chain. It has essentially the same clinical effect as progesterone,<sup>6-11, 20</sup> that is, in the endometrium of the human uterus it causes secretory or progestational development. This endometrial change suggests several possible uses.

Regarding the use of progestational substances, B. Zondek and Rozin<sup>12, 18, 21</sup> claim that it is "possible to induce menstruation solely by injecting progesterone or by oral administration of pregnenolone,† i.e., without preliminary estrone treatment." The dose used is rather large, and the oral dose is considered by them to be five times that of the intramuscular dose. They also claim that with primary amenorrhea or with castration amenorrhea progesterone alone does not cause hemorrhage. Thus, the patient's ovaries must be secreting estrogen above a certain amount before this treatment is successful.

In using pregnenolone for dysmenorrhea<sup>1</sup> it was noticed that small daily doses (5 mg.) caused some patients with amenorrhea to menstruate, and frequently produced earlier menstruation in those with oligomenorrhea. Prior to this it was believed that larger doses were necessary to initiate bleeding in the presence of adequate estrogenic substance.<sup>13, 14, 15, 17, 19</sup> It thus seemed worth while to try this treatment with adolescent girls who had symptoms associated with late menstruation, for which they requested treatment.

It is realized that the effect of pregnenolone on menstruation is largely temporary, but temporary relief is probably all that is necessary, as spontaneous improvement usually occurs in a few months or a few years. Improvement in the endometrium due to pregnenolone may also be beneficial. There is no doubt of the psychologic aid that follows the initiation of menstrual bleeding.

## Clinical Material

Forty-six adolescent girls ranging in age from 11 to 19 years were treated. They were all single. Five had never menstruated. The others menstruated irregularly, thirty-two always late, and nine usually late. Their first menstruation had occurred from a few months up to six years previously, and their ages at the onset of menstruation and at the time treatment was started are listed in Table I.

Most of the patients had symptoms which they believed were due to late menstruation or "trying to menstruate." These complaints varied in different

\*Oligomenorrhea refers to late menstruation, not to scanty menstruation.

†Pregnenolone and pregnenolone are synonymous terms. This preparation is also known as anhydrohydroxy progesterone.

## Discussion

Late menstruation in the adolescent girl can frequently be managed by advice and observation. When the child has been menstruating for several years, is more than sixteen or seventeen years of age, or has severe incapacitating symptoms that do not respond to psychological therapy, exercise, heat, or simple home remedies, it may be considered advisable to institute treatment. In this case the method described is a simple and inexpensive form of endocrine therapy that frequently gives relief. It has none of the obvious disadvantages of the administration of parenteral therapy<sup>3</sup> or of large doses of sedatives and analgesics.

In the presence of sufficient estrogenic substance, the small 5 mg. daily dose initiates uterine bleeding. This makes it unnecessary to use the larger dosage needed for more complete progestational changes that can be demonstrated by endometrial biopsy. Since pregnenolone is given until the bleeding occurs, menstruation starts during treatment rather than after withdrawal. Thus, small dosage initiates uterine bleeding, although it is said<sup>6-16</sup> that larger dosage inhibits bleeding and delays menstruation with the onset of the menstrual period occurring three or four days after its withdrawal. One theoretical explanation of this difference takes into consideration the assumption that small amounts of progesterone aid in the metabolism of estrogen, reducing its effect, and thus act in the manner of partial estrogen withdrawal. Larger amounts of progesterone inhibit bleeding, as they are known to prevent estrogen deprivation bleeding.<sup>10</sup>

Although not a part of this clinical report, it may be stated here that it is usually possible to prime the endometrium with estrogen, and that pregnenolone in 5 mg. doses will then help initiate bleeding. It is well known that withdrawal bleeding will usually occur after giving large doses of estrogens without additional treatment. However, bleeding does not come on as soon and is not as easily controlled as when pregnenolone is added.

Giving the tablets from the eighteenth day of the cycle until bleeding begins usually causes menstruation on about the twenty-ninth day. Starting the treatment earlier in the cycle frequently causes bleeding to occur too early.<sup>1</sup> The small dosage and beginning the medication after ovulation has occurred prevent disturbance of ovulation. It is realized that many menstrual periods in girls at puberty are physiologically anovulatory.

The poor result regarding the menstrual cycle obtained with the five girls who had never menstruated and the six patients with secondary amenorrhea who had not menstruated for six months or longer is due to the lack of sufficient estrogen to cause bleeding. Therefore, benefit usually could be expected only in patients whose last menstrual period had occurred less than six months earlier. The good result, inducement of menstrual bleeding in 87 per cent of the patients with cycles of three months or less is expected, as it is shown by hormone assays<sup>2</sup> that patients of this type have a higher urinary estrogen than those with cycles of six months or longer. This better level of estrogen occurs in those menstruating more often, even though these patients are frequently not ovulating prior to menstruation.

patients and consisted of cramps, aching, and bearing down in the pelvic area, soreness of the breasts, mental depression, and numerous types of nervous symptoms.

Both parents and children thought that the absence of menstruation was abnormal, and there was no doubt but that it created psychological problems.

The condition in all patients was considered functional as no organic pathology was found on examination. Each girl's uterus was small and underdeveloped, and either corresponded with the size to be expected for the child's age or was smaller.

### Method of Treatment

The pregnenolone\* was administered orally in 5 mg. tablets. The daily dose was 5 mg. in forty patients, 10 mg. in five patients and 15 mg. in one patient. The tablets were usually administered from the eighteenth day of the menstrual cycle until bleeding started. Patients not menstruating were either treated for ten days each month or continuously until menstruation started. For further details see Table I.

No sedatives or analgesics were administered during the treatment with pregnenolone. Other glandular treatment was given to some of the patients after observing the effects with pregnenolone, but the results were not included in this study.

### Results of Treatment

Thirty-two of forty-one adolescent girls with oligomenorrhea or secondary amenorrhea showed improvement in their menstrual cycles (Table I). Thus, 78 per cent of the girls with late periods had cycles nearer the twenty-eight day ideal. Of the five patients who had not menstruated in over six months, only one patient had periods while taking the treatment. This girl had cycles averaging from thirty to thirty-five days. Of the three patients with cycles longer than three months and shorter than six months, two had menstrual periods. Of the thirty-three patients with cycles of three months or less, twenty-nine, or 87 per cent, showed improvement. A follow-up record was obtained for six months or longer after discontinuing treatment on thirty patients, whose menstrual cycles had improved, and of these, eighteen reverted to longer cycles. The length of cycle was considered to be accurate because each patient kept this information on a card† containing one year of twenty-eight-day cycles.

The treatment was unsuccessful with the five girls who had never menstruated.

Of twenty-two patients with dysmenorrhea, sixteen were improved, but one was worse. Most of the patients who benefited only received relief for each period immediately following treatment. Of twenty-two patients with various nervous symptoms, fourteen were benefited. Most of these nervous patients had complained of symptoms when the menstrual periods were late. There was definite psychological improvement when the patients menstruated on time. One patient with severe premenstrual cephalalgia obtained marked relief, another adolescent believed that the tablets lessened her enuresis, and a few girls did better work in school. Several patients with facial acne were not benefited; two were made worse. One of the older girls married and became pregnant during the period of treatment.

\*The pregnenolone (Pranone) was obtained from the Schering Corporation, Bloomfield, New Jersey.

†Supplied through the courtesy of Mead Johnson & Co., Evansville, Ind.

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Although little more than temporary benefit could be expected, 40 per cent of the patients with improved cycles continued to menstruate about on time. Some of the others undoubtedly will improve when older.

Pregneninolone has none of the properties of a sedative or analgesic, and, when used in the above manner, works by preventing the occurrence of the symptoms rather than by relieving them. This benefit may be obtained during some months more than others. One must not, therefore, be discouraged by an occasional bad period, whether at the beginning of treatment or during subsequent months. Usually, benefit is obtained with the first month of treatment and with most of the months treated thereafter.

The 72 per cent prevention of dysmenorrhea shown here compares favorably with 73 per cent benefit with pregnenolone reported in a previous study of this problem.<sup>1</sup>

Two patients thought that pregnenolone caused an increase in facial acne. As this substance is also called ethinyl testosterone, and has very slight androgenic activity, this occurrence may have been more than a coincidence.

Mental hygiene should not be overlooked by those giving endocrine therapy. Prevention is still the best form of treatment, and it is ideal to start preventive measures in the child, where the seeds of an adult neurosis are frequently sown. Therefore, the psychological benefits resulting from the initiation of menstrual bleeding, and the avoidance of unpleasant symptoms should not be minimized.

### Summary

Pregnenolone may be used for the treatment of oligomenorrhea and secondary amenorrhea in adolescent girls. It is beneficial for some selected patients, particularly those with severe nervousness or dysmenorrhea when advice and observation do not suffice. For the patient who obtains relief from the use of pregnenolone, its administration is believed to be preferable to parenteral endocrine therapy or to large dosage with sedatives or analgesics which may be harmful. This hormone is given to prevent the occurrence of symptoms rather than to relieve those present. The initiation of bleeding has a psychological advantage.

Forty-six girls were treated. Twenty-nine, or 87 per cent, of the thirty-three girls with cycles of three months or less were improved. Pregnenolone is not recommended for those with cycles of longer than six months or for primary amenorrhea, as results were poor in these groups.

Although the effect of taking pregnenolone tablets is largely temporary, a follow-up record of thirty patients with improved menstrual cycles showed that twelve, or 40 per cent, continued to menstruate regularly and approximately on time during the six months following completion of treatment.

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TABLE I. INFANT DEATHS FROM DIARRHEA

AGE AT DEATH (DAYS)	DATE OF DELIVERY	BIRTH WEIGHT	LAST WEIGHT	BREAST FED	REMARKS
34	Aug. 26	4-7	4-4	No	Twin. 280,000 U. penicillin
23	Aug. 26	5-6	4-11	No	Twin. Purodigin 0.2 mg. b.i.d.
25	Sept. 3	5-15	4-7	No	Purodigin 0.2 mg. b.i.d.
11	Sept. 4	6-5	5-4	No	Signed release; died in another hospital
12	Sept. 5	7-9	5-2	No	Sulfadiazine. 45,000 U. penicillin
34	Sept. 7	7-1	4-14	4 days	Discharged but later returned and died. Sulfadiazine
25	Sept. 16	6-3	5-12	No	Sulfaguanidine. <i>B. coli</i> , streptococcus
20	Oct. 1	6-10	5-6	No	40,000 U. penicillin
12	Oct. 5	6-6	5-3	No	Discharged and readmitted. 90,000 U. penicillin

TABLE II. INFANTS RECOVERING FROM DIARRHEA

DATE OF DELIVERY	DAYS IN HOSPITAL	BIRTH WEIGHT	DISCHARGE WEIGHT	BREAST FED	REMARKS
Aug. 16	24	5-4	5-14	No	60 c.c. plasma, 80 c.c. blood. <i>B. coli</i> , staphylococcus
Aug. 17	16	5-15	5-7	Yes	160,000 U. penicillin. <i>Staph. albus</i> , streptococcus
Sept. 3	13	7-4	7-4	No	Signed release
Sept. 13	10	6-8	6-12	Yes	Readmitted. 80 c.c. plasma. Staphylococcus, streptococcus
Sept. 14	12	5-12	5-0	No	<i>B. coli</i> , streptococcus
Sept. 15	15	6-15	6-15	No	Received some sterilized breast milk. <i>B. coli</i> , streptococcus
Sept. 16	20	5-13	5-10	No	Staphylococcus, streptococcus
Sept. 16	9	6-12	6-7	Yes	<i>B. coli</i> , streptococcus

TABLE III. EPIDEMIC OF DIARRHEA OF THE NEWBORN

	CASES	DEATHS	RECOVERED
Breast and bottle fed	4	1	3
Bottle fed	13	8	5
Total	17	9	8

exclusively bottle fed. In the larger group occurred only four of the 17 cases, one of the nine deaths, and three of the eight recoveries, while in the smaller bottle-fed group occurred 13 of the 17 cases, eight of the nine deaths and five of the eight recoveries (Table III).

During the month of September, I had 33 private cases (included among the 143 deliveries), and I insisted that every mother nurse her baby. There were three that were not breast fed. One mother was very obstinate and refused to nurse, and hers was the only baby among the 33 to develop diarrhea and die. The babies were located in all of the nurseries, and it would seem that if diarrhea was infectious or contagious, more of these 33 babies would have developed the disease. The conspicuous difference between the 32 who did not contract diarrhea and the one who did was that they were breast fed.

### Bacteriology of the Infant Stools

Anderson and Nelson<sup>1</sup> collected from the literature 40 articles, in which 3,065 cases of epidemic diarrhea of the newborn were reported, with 1,291 deaths, a mortality of 43 per cent. They felt there was marked variation in the severity of the epidemics and report one in which 26 infants developed diarrhea with one death, and that in a premature. No mention is made as to whether the babies were breast or bottle fed. During this epidemic, they examined the stools of

## EPIDEMIC DIARRHEA IN THE NEWBORN

### The Relation Between Breast and Bottle Feeding and the Early Development of the Proper Intestinal Flora

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EPIDEMIC diarrhea has been the most dreaded of all diseases of the newborn. The cause has most often been laid to a virus, and the treatment has been of little benefit in reducing mortality. Hospital measures to prevent and combat epidemics have put many restrictions on doctors and on visitors. much valuable space in the nursery has been given over for the isolation of suspected cases, and during epidemics hospitals have been obliged to close. Any measure promising effective control would be welcome.

In this paper I am suggesting that the disease is caused by a metabolic disturbance due to lack of proper intestinal flora. This lack may be caused or prolonged by sterile conditions of delivery and subsequent nursery care. In the presence of these conditions the method of choice for establishing essential bacteria in the newborn's intestines is breast feeding. An epidemic is reported in which most of the cases, and all but one of the fatal cases, occurred in exclusively bottle-fed infants.

#### Report of Epidemic

In late summer and early fall of 1945 there was an epidemic of diarrhea of the newborn at the Methodist Hospital, Brooklyn. In all, there were 17 cases of the disease, with nine deaths and eight recoveries, a mortality of approximately 50 per cent. Of the nine deaths, one occurred in an infant that was partially breast fed; this infant was nursed for the first four days only. The remaining eight were exclusively bottle fed.

The nine deaths (Table I) were not limited to any one nursery, four occurring on the private floor, one on the private ward, and four on the ward floor nursery. Three of the babies died, one on the eleventh and two on the twelfth day; one lived twenty days; five lived longer than three weeks. Even though half of the babies lived for more than three weeks, the average weight loss for the nine babies was  $19\frac{1}{2}$  ounces. Penicillin was used in four of the babies with no apparent improvement. One of the babies went to another hospital, where death occurred, and two were discharged and later were readmitted and died. The most noticeable fact is that only one of the babies was breast fed, and that for only four days.

There were eight newborns that developed gastroenteritis and recovered. (Table II.) Three of these received some breast feedings; one had some sterilized breast milk; the remaining four were exclusively bottle fed. One baby was transfused with plasma, and one received both plasma and a blood transfusion. The babies averaged  $13\frac{1}{4}$  ounces below the birth weight when discharged.

The relation between the incidence and course of the disease and method of feeding can be seen in a breakdown of the 143 living infants delivered during September, 1945, when the majority of the cases occurred. Of these 143 newborn infants, 116, or 81 per cent, were both breast and bottle fed, 20 of the 116 being entirely off breast within ten days after birth; 27, or 19 per cent, were

\*This study was aided by a grant from the John H. Lindrich Fund for Research in Obstetrical Pathology.

## Establishment of Proper Intestinal Flora

How then do essential bacteria reach the intestines of the babies? Undoubtedly, considerable bacteria are collected in the mouth and nose of the baby during birth. Very soon after delivery the baby is supposed to go to breast, and since the mother's breast is not supposed to be sterile, the baby should receive many essential bacteria from this source. If the baby is not breast fed, the raw breast milk or certified raw cow's milk would aid in establishing a suitable intestinal flora. The thermometer by which the temperature is taken, if not properly sterilized, as occasionally happens, may transfer essential organisms from one baby to another. The nipple of the bottle, if the baby receives bottle feedings, though properly sterilized, may collect some bacteria before or during the feeding. It is true that in children and adults most of the organisms taken in by way of the mouth are destroyed before reaching the large intestine, but this may not be true so far as the newborn infant is concerned. Nature may have intended that in the newborn such organisms should not all be destroyed by the acid condition of the stomach and the intestinal ferments, so that the contents of the large intestines might be inoculated with essential organisms. The stomach of the baby is small, and undoubtedly much of the food taken in passes directly into the small intestines. It is easily conceivable that many bacteria taken into the mouth with the food during the early days of the child's life pass quickly into the intestines and are not destroyed. The beneficial bacteria that get there presumably combat pathogenic organisms which, if unopposed, may cause disease, possibly gastroenteritis.

It is evident that babies delivered by cesarean section or following the sterilization of the vagina during labor, who are kept in sterile surroundings and not put to breast, but fed on evaporated milk or boiled formula and given sterile water, experience considerable difficulty in getting the proper intestinal flora established. Therefore, we may be justified in such cases in deliberately inoculating the contents of the large intestine directly from a normal child, or, better still, with a culture of the essential bacteria, which could be easily instilled into the rectum. The best and easiest method of establishing the necessary intestinal flora, however, is breast feeding.

Twenty years ago, before we began the use of vaginal antiseptics at the Methodist Hospital, we were not troubled with epidemic diarrhea. At that time, too, the babies were almost all breast fed and often went to the breast every two hours instead of every four hours, as at the present time. All formulas were very weak, which also encouraged breast feedings, and the babies were under the care of the obstetricians.

I have been stressing a metabolic disturbance due to lack of the proper intestinal flora as a probable cause of diarrhea of the newborn, and breast feeding as the best and easiest means to establish the flora and prevent the disease. Most pediatricians do not name a metabolic disturbance as the probable cause, but say the disease is caused by a virus. If this is the cause, then it must be carried to the nursery by someone who comes in contact with it. The factor of carriers may have some bearing on the occurrence of the disease, and should certainly be taken into consideration. The relationship, however, between breast feeding and immunity or recovery, as discovered in our experience at the Methodist Hospital, seems to merit further investigation and report.

### Summary

1. Epidemic diarrhea of the newborn is usually attributed to a virus, carried to the nurseries by those coming in contact with the disease, and once there rapidly spreading from infant to infant.

2. A probable cause of the disease is faulty metabolism, in turn caused by lack of proper intestinal flora. Beneficial bacteria in the infant's intestines may serve to combat the pathogenic organisms producing the disease.

infants who had the disease for pathogenic bacteria, but the only organism they found with any regularity was a gram-negative bacillus of the paracolon group.

In 1934, Hall and O'Toole<sup>2</sup> examined specimens of the meconium passed by 50 newborn infants, and found that 94 per cent of the specimens failed to show any bacteria on microscopic examination, but 36 per cent showed bacteria when cultured. They found that presence or absence of bacteria was not affected by ruptured membranes.

In 1936, Snyder<sup>3</sup> reported that within thirty minutes after delivery bacteria were present in the stools, and within two hours the majority of the stool specimens were shown to contain bacteria if enrichment methods of culture were used. He was able to isolate 15 different organisms. During the same year he<sup>4</sup> was able to recover *B. welchii* from the duodenum, ileum, and ascending colon of 27 stillborn infants. In all, 16 species were isolated from the intestinal contents of these babies.

From September 13 to October 26, 1945, during the outbreak of epidemic diarrhea of the newborn at the Methodist Hospital, Brooklyn, smears and cultures were taken from the stools of eight babies who developed diarrhea (Tables I and II) and in five *B. coli* was found, in seven streptococcus, and in four staphylococcus. The normal infant's stool does not contain either staphylococcus or streptococcus, and the question arises as to why these organisms were found in the stools of infants with diarrhea. A possible explanation is that the infant could not combat the organisms because of a failure to establish essential intestinal bacteria, which in turn may have been caused by sterile conditions at birth, as in cesarean section or vaginal antisepsis during labor, and by the sterile conditions of their subsequent care.

At the Methodist Hospital we routinely instill the birth canal during labor and at the time of delivery, and there is no doubt that in doing so we destroy most of the bacteria which are found in the vagina. Vaginal antisepsis is an excellent means of keeping the mother from becoming infected following delivery, but it robs the baby of the bacteria it is supposed to collect during its passage through the vagina at birth. Under normal circumstances, when a baby is born without vaginal sterilization, bacteria may reach the baby before birth and during delivery. Nature may have planned that the birth canal should be close to the rectum so that the baby might obtain essential bacteria immediately when born. In the animal kingdom there is no doubt that the intestinal bacteria of the mother are ingested by the young while suckling, since the breasts or udders are almost continually in contact with excreta when the animal is lying down.

Because the meconium is supposed to contain organisms essential to digestion, we took several cultures from the rectum of babies delivered following the use of vaginal antiseptics during labor and at birth, and in no case did we find any gram-negative organisms, the normal organisms which should be in the intestines of the newborn infant. Most of the cultures were sterile, a few had staphylococcus, undoubtedly due to carelessness in taking the culture. In addition, to justify our procedure of doing low classical cesarean sections after the patient has been instilled during labor, and to prove no unnecessary risk is involved, 23 cultures were taken from the heads of babies so delivered immediately following delivery. This was done in preference to taking uterine cultures because of the difficulty of getting a proper culture in the presence of the bleeding which so promptly follows delivery of the child. In none of the cultures were gram-negative organisms recovered, in three a staphylococcus was found, undoubtedly a contamination. If no gram-negative organisms were found, as was the case here, it would seem that there could be little chance of essential bacteria such as the *Bacillus coli* or the *Bacillus bifidus* reaching the intestines before birth.

## PELVIC EXAMINATION FOR NURSES\*

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**P**HYSICAL examination and health supervision of the nurses in our hospitals have been rapidly extended in the last few years.<sup>1</sup> This is the logical result of the rapidly growing interest in preventive medicine and public health. The appalling rejection rate in the armed forces for both men and women is a challenge to us as a profession to find the reasons for and means of combating such a high incidence of actual and potential disease in our future parents of tomorrow.<sup>2</sup>

Examinations of large groups of women employed in industry during the war<sup>3-6</sup> have emphasized the pressing need for recognition of these defects in health and the increased operating efficiency following their correction.

Beginning with the rather cursory preliminary physical examination of earlier days, and progressing through x-ray examinations of the chest and gastrointestinal tract, inoculations against infectious disease, electrocardiograms, blood counts, and blood pressure readings, the student nurses' health departments of modern hospitals have gradually increased their health supervision at least to the time of graduation.<sup>7</sup> These efforts should be extended in scope to include the prepubertal period as well as the remainder of her professional career.

Increasing nursing efficiency and decreased absentee days during the past emergency have undoubtedly resulted from early recognition and treatment for disease. A sick nurse is usually a poor nurse. A nurse who has had illness that has been corrected will be correspondingly more efficient in her understanding and care of her patients' problems. A well nurse who at regular intervals has reassurance about and correction of her health problems will be better able to give diligent thought to her studies and care to her patients.

This formal training of the nurse concerning the value of complete routine physical examination, we believe, will become one of the most important parts of her curriculum, and will enable her to pass this knowledge on to her patients with considerable authority.

During long hours of close contact with the patient, the nurse has more opportunity and, it seems, sometimes more influence on the patient's psychology of health protection than does the doctor. Our problem of the early recognition and cure of cancer must depend on educating the laity and the medical and nursing professions in the importance of complete routine physical examination.<sup>8-10</sup> Many of these defects undoubtedly have their beginnings in utero, and extend throughout the periods of childhood and adolescence. The obstetrician and gynecologist should have as important a role to play in

\*Presented before the 579th regular meeting of the Chicago Gynecological Society, April 19, 1946.

3. It has been proved that infants begin to acquire the essential intestinal bacteria at birth and even before, but babies delivered following vaginal anti-sepsis during labor and at the time of delivery, a routine procedure at the Methodist Hospital, and those born by cesarean section, have been found to have no bacteria in the intestines, either at birth or soon after. The conditions of their subsequent care, sterile water, boiled formula, immaculate surroundings, and so on, make for further difficulty in their establishing the proper flora.

4. Breast feeding is the method of choice for introducing beneficial bacteria into the intestines of these infants.

5. For newborns who cannot be nursed, raw mother's milk and raw certified cow's milk are recommended as richest in beneficial bacteria. The inoculation of the large intestines or the rectum with essential bacteria may also be indicated.

6. An epidemic of 17 cases is reported. There were nine deaths and eight recoveries, a mortality of over 50 per cent. Of the nine who died, eight were bottle fed, the ninth breast fed for only four days. Of the eight who recovered, five were bottle fed, three both bottle and breast fed.

7. In a total of 143 living infants delivered during the month of September, when most of the cases occurred, 116 were both breast and bottle fed, and 27 bottle fed, a proportion of 81 per cent and 19 per cent. In the 17 cases of diarrhea, 13 occurred in the group of bottle-fed infants, with eight deaths; and four in the group of breast and bottle fed, with one death.

8. In this same month there were 33 personal cases. Breast feeding, entirely or partially, was prescribed and carried out in all but three cases, and the only infant to contract diarrhea was bottle fed. These infants were in all the nurseries of the hospital and were not in the care of the pediatricians.

9. During the epidemic, bacteriologic examination of a number of infant stools was made; streptococcus and staphylococcus or both were found in many instances.

### Conclusions

Apparently a cause and effect relation exists between breast feeding and resistance to diarrhea of the newborn. Further investigation of our conclusions seems to be warranted. These are: that early establishment of the proper intestinal flora serves to combat the pathogenic organisms causing epidemic diarrhea of the newborn, and that breast feeding is the method of choice for introducing beneficial bacteria into the newborn infant's intestines; that infants exclusively breast fed should be immune to the disease, those exclusively bottle fed most susceptible, and those receiving some breast feeding able to recover if the disease is contracted; that in the presence of a threatened epidemic, inoculation of the large intestines or rectum with beneficial bacteria may confer immunity if the baby is not breast fed.

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eagerly accepted. It has seemed to me that our profession is trailing far behind lay opinion in its eagerness to avail itself of medical advances in this field of preventive medicine.<sup>11</sup>

This report details the major and minor deviations from normal in the pelvic organs and their physiology of 381 student nurses. These examinations were made by one individual so that re-examination would have an authentic background. Due to the time required and exigencies of the period of war, the re-examinations have not been routine as they should have been, but only for those individuals where findings indicated it. We have later to check the three-year developmental period of training by routine pelvic examinations each six months.

It was quite apparent that the preliminary history given by these girls concerning regularity, duration, and amount of menstrual flow was as inaccurate as the usual one obtained in a gynecologist's office.<sup>12, 13</sup> The history of disability from dysmenorrhea and presence of leucorrhea was particularly inaccurate, because the applicant had felt that pelvic complaints above all others carried a stigma, and would be most likely to cause rejection for training. Attempts have been made to overcome these ideas and to instruct all of these girls in the importance of accurate observation by themselves of one of the most important of their bodily functions. This training has borne fruit in subsequent decisions concerning therapy, and many minor and a few major defects in physiology have been uncovered by this more scientific observation.

TABLE II. AGE

17-22 years	344
23-30 years	28
30-34 years	9
Total	381

The average age in this series is comparable to the greatest number of male inductees examined for our armed forces during the past war. The high incidence of major and minor disease is approximately that found in our young men by careful physical examination.

The standards used to determine the normal weight at the respective age levels were the usual ones followed in nutritional diseases. A deviation of 6 pounds on either side of normal has been allowed for differences in skeletal development or the transitory increment of food and fluid.

TABLE III. WEIGHT

Normal weight	82
Normal findings	
Normal weight	
Abnormal findings	115
Underweight	
Normal findings	21
Underweight	
Abnormal findings	86
Overweight	
Normal findings	16
Overweight	
Abnormal findings	61



their prevention and correction as does the pediatrician. Nutritional and hormonal imbalances in the expectant mother may cause even more pronounced fundamental deviations from normal in her offspring than the emotional disturbances which she occasions in her growing child. In addition, many of the common defects in development and physiology which need correction must be detected early in life before the die is cast in the adult pattern. Routine complete physical examination of the adolescent girl for study and cure of disease offers one of the most fertile and important fields of preventive medicine today. Hospitals, and medical and nursing schools, should lead the way in this development.

In our own training school until very recently, pelvic examination was not included in a rather extensive physical checkup unless the applicant gave a definite history of major gynecologic difficulty. This neglect was based on the antiquated belief in the existence and importance of the intact hymen. We have found both nurses and their parents very receptive and appreciative of these efforts in their behalf.

TABLE I

Unmarried	360
Married	21
Requested examinations	65
Referred from other schools	3
Examined in private office	8

In the entire group, only one nurse has refused or objected to examination. The following week this individual requested examination of her own volition. In addition, 65 nurses who had preceded the initial group in training requested an examination. Most of these requests were not by nurses with pelvic complaints. In addition, three were referred from outside nursing schools, and eight came to the office for examination. Whenever the hymeneal ring was too tight for the usual painless rectovaginal procedure, a recto-abdominal examination was done. The individual was informed that this type of examination was less accurate than the rectovaginal method, and investigation under gas was suggested. Thirty-six returned for this gas examination. In addition, even if the rectovaginal examination was possible, but the hymeneal ring was too tough, tight, or so constricted that it might later cause dyspareunia, dilatation under gas was advised before marriage and offered at this time. Seventeen availed themselves of this opportunity. Many of these hymeneal rings were markedly cribiform, or the high posterior plate brought the opening far forward just beneath the urethral orifice. In this group infantilism, retroversion, and erosion were very frequently found. At the time of the hymeneal dilatation, cauterization of the cervix was performed when indicated. Recognition of these defects in development earlier in life might have offered more physiologic methods for correction by adjustment of the hormonal and nutritional balance.

Almost without exception, the nurse has shown evident relief and pleasure when informed that her genital organs seemed to be normal. When disease has been detected, measures for correction have for the most part been

toms of thyroid insufficiency, such as dry hair, skin, and nails, bradycardia, fatigue, and sensitivity to cold were present and improved along with the menstrual disturbances with thyroid therapy, although the basal metabolism determination was within normal limits. Several of the more severe hirsutisms were also associated with evidences of lowered metabolism and other signs of glandular dyscrasia. Thyroid and theelin therapy seemed to cause some improvement. Electrolysis rather than plucking the unsightly hair caused psychologic improvement, if not retardation of hair growth.

TABLE VI

Ovarian cysts	
Simple follicular	3
Multilocular cystadenoma	1
Dermoid	2
Chocolate	6
Corpus luteum	1
Hirsutism	10
Thyroid imbalance	
(-11 to -30)	19
(+11 to +18)	5

Four of these women had had previous oophorectomies before they entered training. If we add these to the ovarian pathology encountered during our examination, the rate of ovarian pathology is quite high. All of these tumors of the ovary except the large multilocular cystadenoma and three of the endometrial ovarian cysts were removed through the cul-de-sac. In addition, one pelvic abscess and nine appendectomies had been previously performed.

The surgical procedures which we performed, with the indications for them, are shown in Table VII.

TABLE VII

Dilatation of hymen	17
Hymenotomy	2
Dilatation and curettement (for dysmenorrhea)	8
Dilatation and posterior colpotomy (endometriosis or ovarian cysts)	11
Removal of vaginal cysts	1
Laparotomy (endometriosis or chocolate cysts)	3
Cautery of cervix (of 77 Cervical erosions)	41

We have only operated upon those patients with endometriosis when the symptoms and palpatory findings were pronounced, or where progression was evident. There can be little doubt that early recognition and treatment of endometriosis will usually prevent the need for more destructive surgery at a late date.<sup>14</sup> We hope that the correction of some of the nutritional and metabolic disturbances have not come too late to bear fruit in the sexual and reproductive life of these young women. If even a few of them continue, and in turn teach their daughters to have routine pelvic examination,<sup>15</sup> it will not only aid in our fight to control cancer, but prevent other disease as well.

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Using weight alone as a yardstick of nutritional balance, it has become quite obvious that structural and physiologic deviations increase proportionately as we depart from the normal.

Our human machine resembles an airplane. If it is lubricated intelligently and kept on the beam, fewer crashes occur. The nursing supervisors have verified the increased efficiency not only in the hospital but in classwork, as their charges have been brought back on the nutritional beam.

We have arbitrarily divided this group of young women into six series. This division has been made on the basis of normal weights without symptoms or abnormal physical findings as compared with normal weights exhibiting either or both symptoms and abnormalities. The remaining four groups comprise, in like manner, those individuals who were underweight or overweight, with or without abnormal findings or symptoms. As has been previously stated, the total number of entirely normal individuals is low, 119 out of 381, or 32 per cent. There are approximately three times as many abnormal findings in the overweight and underweight groups as there are in those of the normal weight series. There were 197 in the normal weight group, 107 underweight, and 77 overweight. Abnormalities were listed both as symptoms and as physical findings.

The menstrual histories were checked as closely as possible, but it was quite difficult to obtain accurate data from many individuals, especially concerning the quantity of flow. Eight to fourteen pads were chosen as the normal blood loss. Dysmenorrhea requiring medication or bed rest was tabulated; minor cramps were disregarded. Absence of periods for three months or longer was considered as amenorrhea. Several of them had extended for a year or longer. In one instance, the pelvic organs and vaginal mucous membrane were those of an advanced menopause. All of these amenorrheas have been corrected.

The physical abnormalities varied from simple infantile or retroverted uteri to pathology of major importance, such as fibroids, endometriosis, or ovarian cysts as large as a fetal head.

Many of the amenorrheas and oligomenorrheas fell in the group of lowered metabolism and were improved by appropriate doses of thyroid and loss or gain in weight. However, in many of the others, clinical signs and symp-

TABLE IV

Normal menstruation	187
Dysmenorrhea	78
Menorrhagia	83
Oligomenorrhea	64
Amenorrhea	10

TABLE V

Retroversion	57
Infantile uterus or vagina	31
Tight hymen	45
Septate vagina	1
Vaginal cyst	2
Congenital erosion	64
Fibroids	1
Cervical polypi	1
Pelvic inflammation	1
Endometriosis	16
Vaginitis	
Yeast	5
Trichomonas	7

## AN ANALYSIS OF 212 CONSECUTIVE CASES OF ECTOPIC PREGNANCY\*

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**O**F TWO hundred twelve consecutive cases of ectopic pregnancy admitted to the Mount Sinai Hospital since 1915, 172 were treated from 1930 to date, and are the subject of this analysis. From 1915 to 1930, 40 cases were admitted. These were reported in 1929.<sup>1</sup>

In 1944 the Philadelphia Committee on Maternal Welfare reported 101 fatal cases of ectopic pregnancy occurring in the years 1930 to 1943, inclusive.<sup>2</sup> We drew a great deal on the findings of this committee and are indebted to it.

The average age of the 172 cases we are reporting was 34 years. The average stay in the hospital was 14.4 days. With the exception of one, the patients were white. All were operated upon. Forty-five (26.1 per cent) of the cases were in shock when admitted.

*History and Symptoms.*—The classical triad of symptoms, pain, vaginal bleeding, and one or more missed periods were noted 118 times (62.7 per cent). One hundred forty-three patients (83.1 per cent) had pain and bleeding. Of the 172, only two had but a single one of these symptoms. Thirty-nine gave no history of a missed period. Twenty-nine had no vaginal bleeding. A palpable pelvic mass was noted in 62.6 per cent of the cases (116 times). In many of those cases where a mass was not discernible, marked tenderness was noted when the broad ligament on the affected side was put on tension. Too much emphasis cannot be placed on this physical finding.

*Diagnosis.*—One hundred fifty-eight cases were correctly diagnosed before operation; 14 were diagnosed at operation; 47 cases with a working diagnosis of ectopic pregnancy were later proved to have had other pathology. Hence we had 61 failures in diagnosis against 158 correct preoperative diagnoses, a corrected error in diagnosis of 36.6 per cent.

Diagnostic aids were as follows: twenty-seven curettages; six colpotomies; and ten Aschheim-Zondek tests, seven positive and three negative. It is our studied opinion that the greatest single aid in diagnosis is a good history.

*Analysis of Operations.*—Eighty-seven patients were found ruptured; 31 had tubal abortion; 50 were unruptured; there were two abdominal pregnancies (one of these was twins) and two ovarian pregnancies. In the group there were two cases of intra- and extrauterine pregnancies. One had twin pregnancy in the same tube, and three had previous ectopics on the opposite side.

As to the type of surgery performed, there were 82 salpingo-oophorectomies, 73 salpingectomies, 14 tubal resections, and three hysterectomies.

Eighty-two patients (47 per cent) had additional surgery. The end results in this group were the same as in the group that had no additional surgery. Twenty-one surgeons operated on the entire group. Although five of the 21 were residents in training, the results were the same.

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that such damage inevitably resulted when the blood pressure in these dogs dropped to 30 mm. mercury for one and a half to three hours, and that replacement of blood volume after such a lapse of time was useless. Shock became irreversible to blood transfusion.

*Transfusions.*—Of the 90 fatal hospitalized cases in the Philadelphia report, only 42 transfusions were administered to 37 of these patients. Two were given autotransfusion, and 51 were not transfused. Of the forty-five cases in this analysis who were suffering from shock when admitted, all were transfused. The number of transfusions given to this group was eighty-two.

Maintaining blood volume is the most important factor in the ultimate outcome of cases in shock. One may, on occasion, err in diagnosis, surgical judgment, or surgical technique without losing the patient. But delay in combating shock is fatal.

The following case report illustrates this dictum.

Mrs. C., aged 32 years, was admitted in shock. We failed to make a correct diagnosis. On admission her hemoglobin was 40 per cent, and she had 2,190,000 red blood cells. In spite of three blood transfusions given during the first forty-eight hours, her hemoglobin dropped to 36 per cent. Two additional transfusions were administered during the next forty-eight hours. On the ninth day her hemoglobin had risen to 78 per cent and her blood count was 4,150,000 red blood cells. She was symptom free and was discharged from the hospital.

This patient went home and attended to her household duties for six months. She was readmitted with a diagnosis of uterine fibroid. Findings at operation were an old ruptured ectopic pregnancy that had sealed off, massive adhesions, and a great amount of old, clotted blood. She made an uneventful recovery.

### Summary

1. An analysis of 212 consecutive cases of ectopic pregnancy without a death is given.
2. The mortality statistics of ectopic pregnancy are reviewed.
3. Evaluation of therapy is made.

### Conclusions

The greatest single factor in reducing the mortality rate of ectopic pregnancy is early recognition of shock and its immediate treatment.

Next in importance is being ectopic-minded, even if every third or fourth case is erroneously diagnosed. Our analysis shows that for every three correct diagnoses, one was incorrect.

The best aid to diagnosis is a thorough history, with emphasis on the salient symptoms of pain, vaginal bleeding, and one or more missed periods. Eighty per cent of all ectopic pregnancies will give a history of at least two of these symptoms.

Once a diagnosis is made, operate. The amount of surgery done beyond controlling the hemorrhage should be limited not only by the patient's condition, but also by the operator's own surgical limitations. The results in this series have been consistently good, even in the hands of men in training. We

## Discussion of Mortality Rates in Ectopic Pregnancy

Mortality statistics of extrauterine pregnancies present a rather bizarre picture. Our interest in this analysis is mainly focused on this phase of the subject.

The 212 cases covered by this survey were all operated upon and all recovered. We have no mortality to report.

Because of a combined effort by many agencies, the maternal mortality rate in the United States has been reduced from 6.5 per 1,000<sup>3</sup> to 2.4 in 1943, the last available federal statistics.<sup>4</sup> In that same year, 7.2 per cent of maternal deaths were due to ectopic pregnancies.

The Philadelphia report shows a drop in the mortality rate of ectopic pregnancies of 5.6 per cent for the first six years of the study to 3.5 per cent in the last seven years. During the last two years of that study, a further drop of 2.2 per cent was noted.

The Philadelphia report makes the following pertinent observations: of the 101 fatalities studied, 13 were considered nonpreventable. In 58 per cent, responsibility was assigned to the profession. The report lists the following avoidable factors:

- Failure of diagnosis on the part of the referring physician
- Failure of diagnosis on the part of the surgeon
- Delay in operation
- Lack of transfusion
- Poor choice of operative procedure
- Inadequate surgery
- Multiple surgery

We shall now attempt to evaluate and correlate these factors with our findings.

*Failure of Diagnosis.*—A record of 158 correct preoperative diagnoses out of 172 cases would tend to corroborate the Philadelphia Committee's conclusion that failure of diagnosis is an important factor. But our diagnostic acumen must be evaluated against the fact that on 47 traceable occasions we were wrong in suspecting ectopic. Added to the fourteen we failed to diagnose, we have a corrected error in diagnosis of 39.2 per cent (61 cases).

*Treatment of shock and time of operation.*—Of the 101 fatal cases, 90 were hospitalized. Of these, only 65 were operated upon, 21 on admission, 12 within twelve hours, 14 within twenty-four hours, and 18 beyond twenty-four hours. Since all of these cases died, it is presumed that all, or nearly all, were in a state of shock upon admission. In the Mount Sinai group, 45 cases were in shock at time of admission, 39 were operated upon immediately, two within twelve hours, and four delayed because of failure in diagnosis.

There is no question concerning the fact that delay in operation is responsible for many deaths. Yet in our series of 45 cases with shock, four operations were delayed because of failure in diagnosis, one as long as six months. In spite of this delay, the four patients survived. It is our opinion that prompt and effective measures taken to combat shock were responsible for their survival.

Fine, Frank, and Seligman,<sup>5</sup> in a controlled experiment on shock due to blood loss in dogs, recently demonstrated that the diminished blood volume in the portal circulation results in liver damage. They further demonstrated

# PARENTERAL VITAMIN K THERAPY DURING THE ANTEPARTUM PERIOD AND ITS EFFECTS ON THE INFANTS' PROTHROMBIN LEVELS\*

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IN A preliminary report published in 1941, McCready, Callahan, and Grandin<sup>1</sup> discussed the effectiveness, particularly in infants, of parenteral vitamin K therapy administered to pregnant women before the onset of, and during labor. A summary of their findings is as follows:

1. Parenteral vitamin K therapy does not seem to effect the normal prothrombin level in pregnant women.
2. Parenteral vitamin K therapy given during labor caused definite elevation of the blood prothrombin level in 16 of 22 infants.
3. Elevation of the infants prothrombin level seems to occur very quickly after injection in the mother. If more than fifteen hours elapse between injection of the drug and delivery, the effect seems to be decreased.

The vitamin K administered was water soluble, and from the above results we may assume that placental transmission of this substance occurs.

These studies have been continued until a series of 500 cases have been accumulated, which is the substance of this report.

A considerable literature on this subject has sprung up during this interval, and the results have been very encouraging, especially in reference to the prevention of hemorrhagic disease of the newborn. According to Pray,<sup>2</sup> hemorrhagic disease of the newborn occurs in about 0.7 per cent of newly born infants. The usual time of appearance is between the second and fourth days of life. The bleeding, of an oozing type, may come from almost any part of the body, the umbilicus, cutaneous surfaces, and bowel being the favorite sites. Intracranial hemorrhage, hepatic, and adrenal hemorrhage are also common. Willis<sup>3</sup> found, from a study of 476 cases of hemorrhage in newborn infants, that vitamin K therapy yields excellent results in hemorrhage from the digestive tract, umbilicus, and skin.

Hauser,<sup>4</sup> on the other hand, in a study of 2,280 infants receiving vitamin K prophylactically and 2,250 controls, concludes that while vitamin K therapy definitely influences the prothrombin time in infants born at term, it does not necessarily influence mortality from hemorrhage. However, he also states that mortality of prematures in the treated group was only half that of the untreated group, which indicates a marked prophylactic effect of the vitamin K. It is agreed generally that during the first few days of an infant's life a deficiency of prothrombin exists in the circulating blood. According to Butt<sup>5</sup> most workers believe that instances of cerebral hemorrhage occurring in the course of birth with minimal trauma are precipitated by small hemorrhages which endure for

\*This work was done under a grant from the Keufel Fund and Abbott Laboratories. The Vitamin K (Menadione) was supplied by Abbott Laboratories.



attribute this to the fact that unlimited surgical privileges are few, and those who are given limited surgical privileges are carefully supervised.

That we did not have a single death due to embolism or other so-called unavoidable complications, we credit to good fortune.

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1. The thromboplastin was prepared from rabbit's lungs by the desiccation method of Shapiro and his co-workers.<sup>8</sup>

2. One hundred milligrams of this dried thromboplastin was mixed with 5 c.c. saline and inactivated at 58° C. for fifteen minutes. The mixture was then centrifuged slowly and the supernatant fluid used. With a Sahli hemoglobin pipette 20 cu.mm. of blood was drawn from a small incision in the infant's heel, and blown into a hollow ground slide already containing 20 cu.mm. of the inactivated thromboplastin solution prepared above. The stop watch was started at this moment, and the blood thromboplastin mixture was stirred with a fine wire loop until the clot appeared. The stop watch was stopped at this point and the time in seconds noted.

Fig. 1 shows a composite curve of the prothrombin levels of our treated cases as compared with cases in which no vitamin K was administered.

In those patients in which no vitamin K was given to the mother or child, the prothrombin levels in the infants start at about forty-five seconds on the first day of life, and rise to about sixty seconds between the second and fourth day, dropping to a normal of thirty-two seconds on the seventh day. The composite curve of the cases treated according to the schedule outlined above start on the first day of life with a prothrombin level of about thirty-two seconds, and, with slight variations, maintain this level throughout the first seven days.

As is the case in any series of experimental observations there were some exceptions. Five cases were observed which maintained a flat prothrombin curve, notwithstanding the fact that no vitamin K had been given either to the mother or child. In these cases the mothers must have had exceptionally large stores of vitamin K, or the infants started to manufacture their own supply unusually early. In three cases out of the 500 in which vitamin K was administered, there was no response in the infants, and the prothrombin levels became elevated on the third and fourth days. In two of these cases the prothrombin levels of the mothers were even better than average. One infant was jaundiced, which may explain the lack of response in that case, but the other two cases are more difficult to understand. However, lack of response in three out of 500 cases is less than 1 per cent, so that we can say that the method of administration of vitamin K as outlined is adequate.

### Summary and Conclusions

1. Parenteral vitamin K therapy does not affect the normal prothrombin level in pregnant women, but its effects in the infant are manifested promptly after injection.

2. In a study of 500 cases, an injection of 20 mg. of hykinone given to the mother before delivery resulted in normal prothrombin levels in 99 per cent of the infants.

3. Vitamin K injected into the mother before delivery or into the infant immediately after birth is the best prevention for hemorrhagic disease of the newborn.

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a few days. For this reason, the lives of some of the infants might be saved if the blood at birth had better coagulation properties. Lehman,<sup>6</sup> in a comparison of deaths from bleeding in 13,250 full-term infants receiving vitamin K with 17,740 untreated cases, showed that 1.6 per thousand could be saved by the treatment.

Williams<sup>7</sup> emphasizes the fact that, due to the precipitous drop in the prothrombin level during the first days of life, hemorrhagic disease of the newborn is a potential threat to all infants. Consequently, if an infant should bleed accidentally, the amount of blood lost may be sufficient to reduce the prothrombin level still further, to a point where hemorrhage becomes difficult to control. The ordinary tests for bleeding and clotting appear to reveal the abnormality of the blood only when the prothrombin deficiency is extreme. It is for this reason that prothrombin estimation of the blood as developed by Quick is so important.

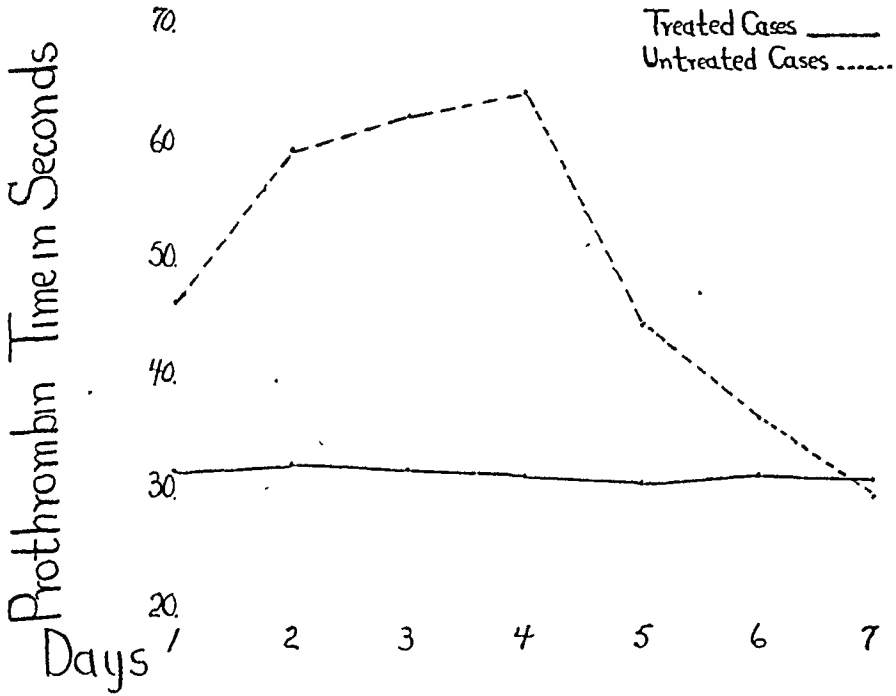


Fig. 1.

Williams is further of the opinion that trauma will continue to be the predominate cause of intracranial hemorrhage of the newborn. His work shows that infants subjected to some degree of injury may fail to develop a significant hemorrhage unless a marked decrease in the prothrombin level is present. Similarly, a mild hemorrhage may become marked as the physiologic decrease in prothrombin develops forty-eight hours subsequent to delivery. It is therefore seen that vitamin K administered to the mother before delivery should afford increased protection to the infant.

Method

In our studies on 500 cases, the following routine was observed. An intramuscular injection of 20 mg. of menadione bisulfite or hykinone was given to every mother before delivery. If the labor was prolonged over twelve hours, this injection was repeated. If the labor was four hours or less the infant was given an additional injection of 2 mg. of hykinone. Prothrombin tests were done on the infants daily for the first week of their lives. The technical details of performing the prothrombin test on the infants are as follows:

out autopsy, not infrequently the diagnosis of pulmonary embolus is incorrectly made. He further believes that this is true not only in obstetrics, but in surgery and medicine as well.

No obstetric accident is quite so tragic and no situation in the entire field of obstetrics quite so distressing as that following sudden death caused by embolism. The confusion and grief of the relatives brought about by the tragic and sudden death make it almost impossible in many instances to obtain an autopsy. Following such a death, autopsy is never more desperately needed to make a correct diagnosis and to aid us in establishing correct classifications for obstetric problems which terminate in death of the patient.

By autopsy, Steiner and Lushbaugh<sup>1</sup> have disclosed a new causation for pulmonary embolus in the puerperium, and this leads us to change our classification of this disease as follows:

Pulmonary embolism in the puerperium produced by: (a) Large thrombi which originate in the maternal systemic venous system. (b) Those thrombi originating in the right side of the heart. (c) Air emboli. (d) Nonfatal pulmonary embolism by placental fragments. This type has been described by Ceelen and associates,<sup>6</sup> and is recognized as a common, if not constant, occurrence by pathologists who have an opportunity to examine lungs microscopically in women dead of other causes in early puerperium. Geipel,<sup>7</sup> in 1928, described 40 personal observations of ectopic decidua formations in the pelvic glands, omentum, diaphragm, appendix, and spleen. (e) Contents of the amniotic fluid. This unusual type of embolism is manifest at autopsy by the microscopic appearance of mucus, vernix, lanugo hair, and meconium in the arteries, arterioles, and capillaries of the lung.

### Case Report

Mrs. E. P., a 33-year-old white para i, gravida ii, was admitted to the obstetric service the evening of March 15, 1946. The expected day of delivery was March 4, 1946. Her membranes had ruptured at 8:30 P.M.; she had a pink show but had not had pain. The history was otherwise negative, and the previous pregnancy had been uncomplicated. The first infant's weight was 8½ pounds, and the labor was six and one-half hours.

Physical examination disclosed a blood pressure of 100/72; her temperature was 36.2° C.; pulse, 88; respiration, 20. The patient was an apparently normal term pregnancy. The examination revealed normal findings, including a fetal heart of 152 in the right lower quadrant. The position of the fetus was right occipitoanterior, the head was floating, and the cervix admitted one finger upon rectal examination. The pelvic measurements were: intraspinous, 22 cm.; intraerestral, 25 cm.; and external conjugate, 19 cm.

This patient presented herself for prenatal care Aug. 22, 1945. On initial physical examination at that time, her chest was clear, and heart not remarkable. Breasts negative, teeth in good repair, and external pelvimetry gave measurements all within normal limits. Vaginal examination found normal structures, except for an old laceration of the cervix. The patient was seen on nine separate visits prenatally, during which the blood pressure ranged from 106/68 to 122/80. Weight showed a progressive gain from 121 pounds to 149 pounds, and complete urinalysis totally negative at all times. Hemoglobin in January, 1946, was 80 per cent. In November, 1945, the patient was placed on a low calorie diet and 1 grain thyroid extract twice a day after gaining 8½ pounds the preceding month. Serologic (prenatal) test for syphilis taken November 28, 1945, was reported negative.

On March 6, the patient presented complaints of headache, dizziness, spots before her eyes, and insomnia. No edema was present. Her blood pressure

## MATERNAL PULMONARY EMBOLISM BY CONTENTS OF THE AMNIOTIC FLUID

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FATAL maternal pulmonary embolism by amniotic fluid and its particulate contents was described by Steiner and Lushbaugh<sup>1</sup> in 1941. A related paper by the same authors<sup>2</sup> followed in 1942. These authors found that the disease clinically was characterized by profound shock, which led in some cases to pulmonary edema, and in others was accompanied by uterine atony and hemorrhage. The essential pathology was found on microscopic examination of the lung. It consisted of widespread embolism of small pulmonary arteries, arterioles, and capillaries by the particulate matter found in amniotic fluid and meconium. They reported that the disease had been duplicated clinically and pathologically in dogs and rabbits by the intravenous injection of those substances obtained from human beings.

Diligent search of medical literature revealed that this case in question is the eleventh of its category to be reported. We owe a debt of gratitude to Steiner and Lushbaugh, who, during their microscopic observations of lung tissue in general autopsies, discovered and reported<sup>1</sup> in 1941 this widespread embolism of small pulmonary arteries, arterioles, and capillaries by contents of the amniotic fluid, i.e., a causation for pulmonary embolism which had not previously been known. All reported cases of this unfamiliar disease were diagnosed upon microscopic necropsy findings, and the above authors report an incidence of fatal cases amounting to 0.2 per cent in general autopsies and 1:8,000 confinements.

The writer, having conducted a study of post delivery deaths caused by embolism in 1935,<sup>3</sup> has been deeply interested in this subject. After completing a review of the causes of maternal death in Cleveland during the five-year period from 1930 to 1934 inclusive, involving 80,136 births, he was greatly surprised to discover that embolism was responsible for 14.5 per cent of the delivery deaths. He found a total of 469 maternal deaths, of which 254 were classified as delivery deaths, i.e., deaths which occurred in mothers whose babies were delivered at or beyond the period of viability. In these 254 delivery deaths, he found 37 post delivery embolic deaths, which represents an incidence of one such death to every 2,138 births included in the survey, or 14.5 per cent of the delivery deaths and 7.8 per cent of the total maternal deaths. Compared to reports of other American cities, these figures were relatively high; for example, New York's three-year survey<sup>4</sup> showed that the post delivery embolic deaths amounted to 7.4 per cent of the delivery deaths, and Philadelphia's two-year study<sup>5</sup> reported 11.2 per cent in the same manner. The fact that this rate was high gave added impetus to this study, which had involved the records of 13 Cleveland hospitals.

In retrospect, after six months spent in contacting the medical staff of 13 hospitals, studying their charted records and checking the death certificates with the Cleveland Bureau of Vital Statistics, the writer found to his great disappointment that causation of death in reference to these 37 embolic fatalities was determined by clinical diagnosis only. Although these records were authentic, and the physicians who recorded their observations and procedures were well trained, sincere, and mature in mind, the writer believes that with-

*Histopathology.*—Microscopic diagnosis of the lungs (Dr. Rafael Dominquez). (1) Acute passive congestion of lungs, slight; (2) edema of lungs, slight; (3) multiple emboli of intrinsic blood vessels of lungs by mucus, and epidermal squamæ (the term "epidermal squamæ" includes vernix, lanugo hair and meconium); and (4) discrete thrombo-embolism of pulmonary vessels.

*Final Pathologic Diagnosis.*—Extensive pulmonary embolism by amniotic material (mucus and epithelial squamæ); term delivery, intrapartum death; and stillbirth.

### Discussion

This case presented the casual multiparous parturient with an uneventful prenatal record, a normal pelvimetry, negative serology, no toxemia, and no past history of systemic diseases, whose labor ended in tragic death. The diagnosis was not disclosed until the lung tissue was microscopically examined at autopsy.

Except for the terminal bleeding from the nose, gums, and subcuticular tissues, the mottled skin, the pulmonary edema under anesthesia (nitrous oxide and oxygen), and the cardiovascular collapse, no clinical diagnosis was made. In this widespread massive type of pulmonary embolism naturally supportive treatment was of no avail.

After the patient had spent forty-eight hours in the hospital, in and out of bed with irregular contractions (mostly Braxton-Hicks) and slight loss of amniotic fluid, 45 c.c. of oleum recini was given. Four hours later labor of moderate severity began with an expulsion of 30 c.c. of blood while on the bedpan. No further bleeding was noticed until delivery. The delivery was spontaneous. Following placental delivery, bleeding was less than normal. There were no new lacerations of the cervix or outlet. There were no signs of uterine rupture. 1,500 c.c. of 5 per cent glucose intravenously failed to cause any drop in a temperature of 40.9° C.

Embolism was mentioned clinically, but was ruled out because she complained of no cough, no chest pain, or discomfort. The cardinal signs of embolism were absent until immediately before death, when she became dyspneic, and finally cyanotic.

In consideration of the confusion of signs and symptoms mentioned above, it was quite evident that clinical diagnosis was most difficult.

### Summary

1. Maternal pulmonary embolism by contents of the amniotic fluid presents a new category for the causation of lung embolism.
2. Ten cases have been reported in the literature.
3. A new case is reported.
4. The diagnosis of all cases have been made at necropsy.

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was 122/80; urine, negative. The general condition was attributed to anxiety, but she was put on a toxemia regime. On March 12, the patient returned; her condition was much improved.

*Course.*—The patient began to have some irregular pains, but these ceased shortly. No further dilatation occurred in the first eighteen hours. This was confirmed by vaginal examination, and x-ray pelvimetry was carried out which showed all measurements were within normal limits.

At 10 P.M., on March 17, 1946, there was castor oil induction. At 2 A.M. on March 18, 1946, while the patient was on the bedpan, there was a sudden discharge of about 30 c.c. of bright red blood (assumed to be from the vagina). There was no further abnormal bleeding. Blood pressure was 108/74; pulse, 92; respiration, 24. The fetal heart was last recorded at 9 P.M., on March 17, 1946, as 132. The fetal heart was not audible at the time of the bleeding, although the fetus seemed unusually active. Blood was drawn for typing and cross match.

At 4 P.M., on March 18, the patient complained of a feeling of chilliness, and her temperature was 38.5° C. At 5:30 P.M. the temperature was 40.3° C., and slight bleeding from the gums was noticed. The patient was very restless, but was not irrational. She was given 1 Gm. of sulfadiazine per os at 5:30 P.M., but was unable to retain it. An intravenous injection of 1,500 c.c. of 5 per cent glucose in water was started at 5:45 P.M.

At 7 P.M., her temperature was 40.9° C.; pulse, 108; respiration, 32. Examination of the heart showed the presence of a harsh, blowing, systolic murmur heard over all areas. This was not present on admission. Examination of the lungs was negative. There was marked bleeding from the mouth, and the lips were parched and dry. Uterine contractions were severe, of two to three minutes and forty-five seconds' duration.

At 8:00 P.M., the patient was taken to the delivery room with the fetal head on the perineum. It was noted that the skin was cooler, mottled, and that the blood pressure was 74/34. The pulse was very rapid and weak, and respirations were rapid and shallow.

At 8:45 P.M., after seventeen hours and forty-five minutes of irregular dry labor, and seventy-two hours and fifteen minutes of ruptured membranes, a stillborn fetus, 7 pounds and 15 ounces, was spontaneously delivered, and very little blood was behind the placenta. The latter had a foul smell, and it was noted that the blood did not clot, so the uterus was packed, even though it responded well to ergotrate.

The anesthetist noticed an increasing amount of blood in the mouth at this time. Even in the state of shock, blood extravasated from the venapuncture wounds into the tissues. Auscultation of the lungs revealed coarse, moist râles, more prominent on the left side of the chest. Respirations ceased just as a cut down was completed for whole blood. Intracardiac adrenalin was given, but the heart continued only a few minutes. Oxygen with the closed bag system of artificial respiration was not successful. The patient expired at 9:30 P.M. on March 18, 1946.

*Postmortem Findings.*—Slight cyanosis and pallor of the nail bed, and there was a yellowish cast to the skin of the face, especially around the mouth and chin. Generally there was a yellowish cast, cyanosis, and pigmentation of the skin. Thorax and abdomen not remarkable. Pleura showed congestion, and several punctate hemorrhages were seen in it. Left lung weighed 350 Gm., and the right, 380 Gm. Upper lobes of both lungs were mottled. Heart weighed 260 Gm. Pericardium when opened contained about 100 c.c. of blood. Spleen weighed 450 Gm. It was markedly enlarged. Liver weighed 1,750 Gm. It was paler than usual. Uterus weighed 1,250 Gm. The fundus reached the level of the umbilicus.

and active *Trichomonas vaginalis*, for which she was given Floraquin suppositories and vinegar douches.

The pelvic pain persisted, and later examination brought up the question of a left-sided pelvic mass. To rule this out, a uterosalpingogram was done one day after the period ceased. The cervix was grasped with a tenaculum and gently dilated. After a Hyams' apparatus had been passed into the dilated cervix and 2 c.c. of iodized oil injected, a roentgenogram was taken. Three more c.c. of oil were injected, and another film was taken; and finally, another 3 c.c. of oil followed by a third roentgenogram. After this, the films were processed. The patient experienced no untoward reaction, and went home the same day.



Fig. 1.—Droplets of oil are visible in the veins of the pelvis. At the upper margin, there are minute streaks of oil which are believed to be in the small vessels of the lung.

The roentgenograms (Fig. 1) showed a large amount of oil in the vessels outside of the uterus with some extension into the ovarian veins. Close inspection of the upper margin of the film revealed numerous minute, linear shadows of increased density which had the appearance of iodized oil in small vessels of the lung.

On the day following, the patient noted a queer feeling in the chest, as though someone was constricting it. On the second day after the injection



## OIL EMBOLISM FOLLOWING HYSTEROSALPINGOGRAPHY

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THE purpose of this report is to record another instance of oil embolism, a serious complication, following hysterosalpingography. The procedure is a rather common, and usually benign examination in gynecologic and roentgenologic practice, but it should be remembered that, like intravenous pyelography,<sup>3</sup> it is not entirely without danger.

A few cases of oil embolism have been published in the American literature,<sup>1, 5, 9</sup> but most of the material on this subject has appeared in journals published outside the United States. Cases have been reported in which, following hysterosalpingography, cough and occasionally blood-stained sputum occurred and were attributed to small pulmonary emboli.<sup>4, 7, 8</sup> Gajzágó<sup>2</sup> reported the death of a 60-year-old woman after hysterosalpingography performed for postmenopausal bleeding. The patient went into shock soon after the injection of Iodipin, at a pressure of 80 mm. of mercury, and died nine hours later. Neeropsy revealed oil emboli in the lungs, heart, and kidneys. A submucous fibroid was found in the uterus, and it was concluded that this may have been a causative factor in the intravasation of the oil into the venous circulation.

In 1923, Sicard and Forestier<sup>6</sup> injected iodized oil into the femoral veins of dogs without harmful effect. The oil reached the pulmonary capillaries, and in ten to twelve minutes had disappeared from them. In other experiments, 2 to 4 c.c. of the oil were injected very slowly into the cubital veins of human subjects. Serial roentgenograms of the chest showed that it reached the pulmonary capillaries within three to four seconds. It remained in the lung in the form of droplets for six to eight minutes, after which it suddenly disappeared. Cough, without dyspnea, was the only untoward symptom noted by the patient.

We have seen two cases at the Massachusetts General Hospital in which oil entered the circulatory system following hysterosalpingography, and in neither of them was it possible to demonstrate subjective or objective evidence of a pulmonary lesion. A third case, seen more recently, is presented in detail to illustrate one of the possible dangers which may be encountered following the injection of oil into the uterus.

### Case Report

B. S. (U-399304), a 43-year-old para iii, complained of pain of several months' duration in the left lower quadrant and in the left side of the pelvis. Associated with the pain was a vaginal discharge with burning and itching. Her periods had begun at the age of 14 years, and were regular every twenty-four days. The flow lasted only one day, and considerable pain was experienced at that time. Physical examination showed blood pressure 128/80, weight 126 pounds, temperature 98.8° F. Her abdomen was soft, and no masses were felt. Her external genitals were normal. The cervix was lacerated and infected; several nabothian cysts were present. The uterus was in third degree of retroversion, was not very movable, and a little roughening behind the cervix suggested endometriosis. Vaginal smear demonstrated pus

on the uterus also increases the likelihood of intravasation, and that uterosalpingography should not be done until eight to ten days after operation on the uterus or following the cessation of menstruation.

In this case 8 c.c. of oil were injected before the roentgenograms were developed. For this reason this whole amount may have found its way into circulation and caused the reaction which we have reported. Actually, the first film, which was taken only after 2 c.c. of oil were injected, showed the oil in the pelvic veins. If this film had been developed and observed further, oil injection could have been avoided.

Since our experience with this case, the time chosen for hysterosalpingography is in the middle of the menstrual cycle, and the technique of the procedure has been modified. As it is at present carried out, 2 c.c. of iodized oil are injected under manometric control, pressure not to exceed 200 mm. of mercury; the roentgenogram is taken, developed, and examined before further oil is introduced. If, and as necessary, more oil is injected and immediate roentgenographic examination is made. Stereoscopic films are taken, and six hours after the injection a film is taken to see if there is free oil in the pelvis.

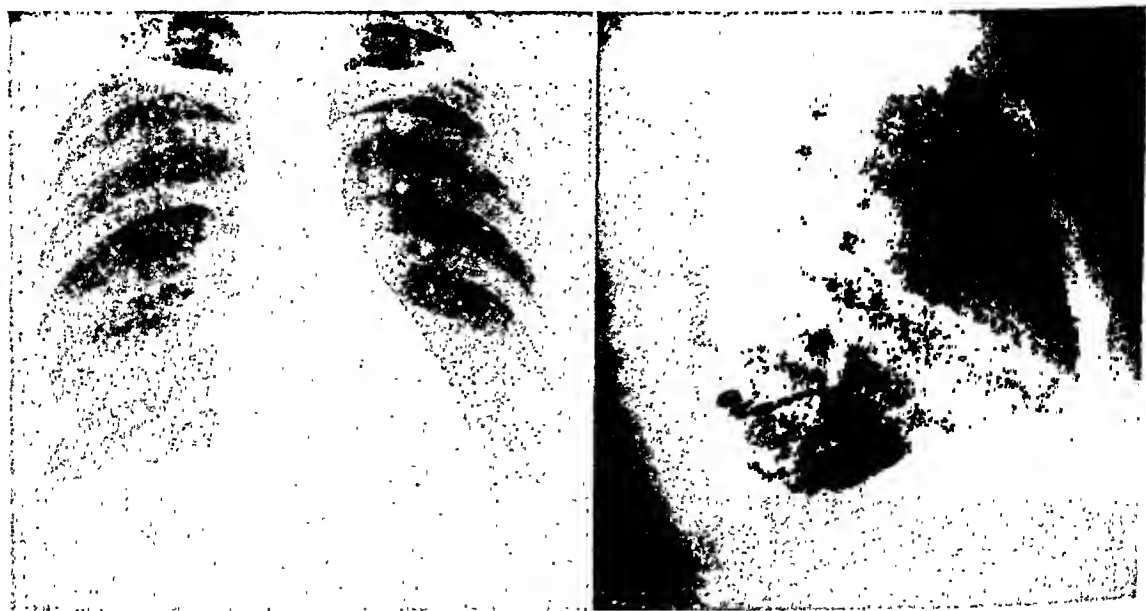


Fig. 3.—Examination of chest nine days later. Roentgenograms show loss of the granularity and decrease in the amount of pleural fluid.

Another factor in this case which may have contributed to the complication is the possibility that the endometrium received direct trauma from the cannula. In the presence of a submucous fibroid or malposition of the uterus, such as marked retroversion, trauma may easily occur as the cannula is introduced, especially if the tip is sharp. If penetration or laceration of the endometrium results, intravasation may follow. The apparatus used in the case presented had as a tip a ureteral catheter, which may possibly have perforated the endometrium and entered a venous sinus. At the present time a blunt tipped cannula is used and the examination has been just as satisfactory. If it seems advisable, the plane of the uterine cavity may be determined by a uterine sound before the cervical cannula is introduced.

It is of considerable importance that close cooperation between the roentgenologist and the gynecologist be maintained in order to prevent intravasation of oil into the uterine vascular channels. The outcome of this case was

of oil, she had pain in both sides of her chest, greatly aggravated by deep breathing, but she had no cough or sputum. She was readmitted to the hospital. Roentgenogram of the chest (Fig. 2) taken seven days after the injection of oil revealed numerous rather patchy shadows of increased density which were consistent with infarets. There was evidence of a small amount of fluid in the pleural cavity. At this time no definite shadows were seen which had the appearance of vessels containing oil. Just before the patient's discharge from the hospital examination showed considerable improvement in the appearance of the chest (Fig. 3).

The patient's temperature had risen to 100.8° F. on the fourth day after injection and had remained elevated for four subsequent days. It then returned to normal. The white count on the seventh day after injection was 8,100; the hemoglobin was 72 per cent. The urine sediment was negative. During the next nine days the pain disappeared, the temperature remained normal, and the patient was discharged. She has had no recurrence of the pulmonary symptoms, and no further roentgenologic examination has been made.

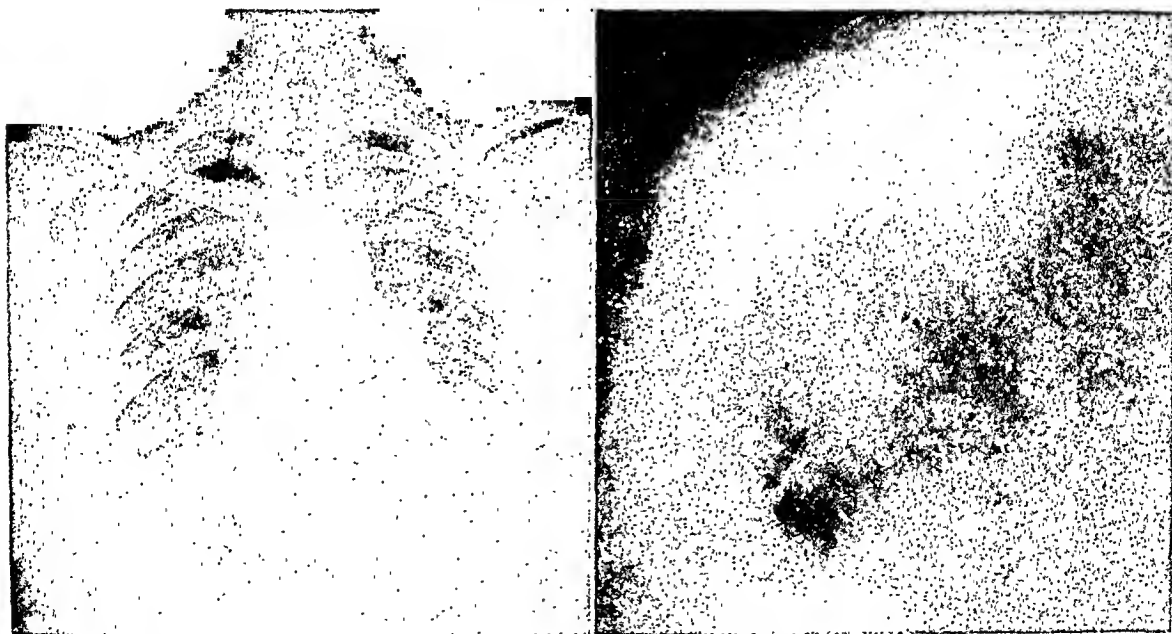


Fig. 2.—Examination seven days after injection of oil. Patchy areas of increased density are seen scattered throughout the lung fields, and there is fluid in the posterior portion of the pleural cavities. The films showed a fine, granular appearance in the lung fields which suggested to the examiner that the shadows were composed of dense rings with bright centers about the size of alveoli.

Certain factors in this case, particularly those regarding the injection of iodized oil, merit comment. Both the times of operation and the amount of oil injected before the roentgenogram was studied may have been ill advised; and possibly the cannula on the Hyam's apparatus perforated the endometrium. The time chosen for hysterosalpingography is important. In this instance the operation was performed the day after the cessation of the patient's period. At this time in the menstrual cycle the endometrial lining is thin and has not been completely regenerated. Intravasation might easily occur under such circumstances. Williams<sup>5</sup> reported six cases seen in one year in which venous intravasation occurred during uterosalpingography. In two cases, the oil had been injected two and four days after menstruation, and in two others, within seven days after dilatation and curettage. This suggests that recent operation

## ESTROGENIC TOLERANCE IN PREGNANT WOMEN\*

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THIS paper is presented in order to report the results of some recent investigative work by the author, which has led us to believe that we may have had an entirely erroneous conception of the action of estrogens in women during pregnancy.

It has been the opinion of most authorities<sup>1,2</sup> that the estrogens act to stimulate uterine muscles and thereby tend to enhance the evacuation of a pregnant uterus. The clinical experience of this author has been decidedly to the contrary. Instances will be cited later in which pregnant women were given massive, 25 mg., doses of an estrogen (diethylstilbestrol). These women all carried their pregnancies to full term and delivered normal babies, as verified by examining pediatricians.

The general belief that estrogens tend to cause abortions grew out of certain animal experimentation which will be outlined below. The results of these experiments have not held true in the case of human beings. Quite to the contrary, the author has come to feel very strongly that the estrogens are an excellent antiabortifacient in humans. Heretofore, it was considered unsafe to administer large doses of estrogens during pregnancy, and in instances of threatened abortion part of the accepted treatment was the administration of progesterone, a substance we were once justified in considering as antagonistic to the estrogen in its action on uterine musculature.

The apparent reason that the medical profession was led to believe that the estrogens were of the nature of an abortifacient was due to some of the following publications:

Parkes and Bellerby,<sup>1</sup> using white mice, reported that they were able to prevent conception and to interrupt pregnancy at any stage, with comparatively small doses (1 to 5 mouse units of stilbestrol), although the dosage needed in the last part of pregnancy was twice as much as that in the first half of pregnancy. Kelly,<sup>2</sup> working with guinea pigs, was able to prevent their conception and to interrupt pregnancy at any stage by the use of estrogen. The fetuses died following the administration of estrogens to the pregnant guinea pigs. He believed that the death of the fetuses seemed to be related to the marked atrophic changes in the chorionic villi, resulting from pressure due to excessive hyperemia or other causes. Kelly,<sup>2</sup> Smith,<sup>3</sup> and Parkes and Bellerby<sup>1</sup> concluded that conception and normal pregnancy are not compatible with an excess of estrogen over corpus luteum hormone in the blood. Smith<sup>4</sup> reported similar findings in rats. Zondek and Aschheim<sup>5</sup> were also able to produce abortion in animals with excessive doses of hormone. Falls, Lackner, and Krohn<sup>6</sup> stated, "It is entirely possible that a deficiency of progesterone or an excess of the estrus-producing hormone would result in spontaneous abortion or premature labor." Parkes.

extremely fortunate, inasmuch as it might have been fatal, as has been reported in other instances.<sup>6, 9</sup>

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did not provoke any of the usual unfavorable effects in these patients which sometimes results in the administration of the drug to nonpregnant women.

Ten patients were each given 500 mg. as a single intramuscular dose, and three were given 1,000 mg. as a single dose by mouth and intramuscularly. In no case did abortion result, nor were there any untoward symptoms due to the sudden large dose administered or withdrawn. All became nauseated and vomited, just as do nonpregnant women. It was determined that 500 mg. or more of diethylstilbestrol in a single dose are required to produce the same nausea and vomiting in a pregnant woman that result from the administration of only 0.75 to 5.0 mg. to the nonpregnant woman. In brief, pregnant women tolerate with ease approximately 1,000 times the dosage of diethylstilbestrol that nonpregnant women do. During pregnancy, the body apparently can metabolize up to 500 mg. of stilbestrol per day, and only 0.5 mg. in the nonpregnant woman. Twelve patients who were experiencing excess morning sickness, voluntarily stated that their nausea and vomiting subsided in from three to five days after the administration of 300 mg. daily for from three to five nights.

Fourteen patients in the obstetric clinic varying from 28 to 168 days of pregnancy were given varying doses of diethylstilbestrol, as shown in Table I.

TABLE I. ORALLY ADMINISTERED STILBESTROL

NO.	PATIENT	NUMBER OF DAYS GIVEN STIL- BESTROL	AVERAGE AMOUNT PER DAY (MG.)	TOTAL (MG.)	DAYS PREG- NANT	EXCEP- TIONS TO NORMAL PREG- NANCY	REMARKS
1	C. A. R.	33	200	6,600	229	None	
2	J. P.	124	50	6,200	183	None	
3	S. E. D.	65	223.84	14,550	102	None	
4	T. A. R.	28	266.07	7,450	63	None	
5	R. B. J.	7	25	175	53	None	
6	D. J.	29	262.07	7,600	107	None	
7	E. E. C.	65	176.94	1,150	243	None	
8	V. W.	19	789.47	1,500	248	None	
9	G. W. H.	67	332.09	2,225	127	None	
10	J. E. E.	68	229.41	15,640	Delivered	None	Baby normal in every way
11	S. J. B.	134	46.79	6,270	Delivered	None	Baby normal in every way
12	L. N. P.	221	69.12	15,275	Delivered	None	Baby normal in every way
13	E. W. H.	179	100	17,900	Delivered	None	Baby normal in every way
14	G. P. W.	22	25.54	562	Delivered	None	Baby normal in every way
Totals		1,061	185.45	103,097			

One patient with threatened abortion who had been "spotting" for eight days came in as an emergency. Her condition was diagnosed ectopic pregnancy because of the pain in her left side over the left tubal region, and spotting. She was rushed to the operating room and an exploratory laparotomy was done. Upon opening the abdomen the patient was found to have about a three months pregnant uterus, which was so spastic and so firmly contracted that it was quite perceptibly blanched. There was no ectopic pregnancy. One hundred milligrams of stilbestrol (4 c.c. in olive oil) were administered directly into the anterior wall of the uterus. The uterus relaxed from its contracted state and assumed the bluish pink color of a normal pregnant uterus. The patient was about three months pregnant. The abdomen was closed and the patient was sent back to the ward. This patient delivered a normal child at term.

A normal patient, five months pregnant, was x-rayed and the uterus could be easily outlined on the x-ray film. Two hundred milligrams of diethylstilbestrol were given into the anterior wall of the cervix. Further x-rays were taken immediately following the injection, and every fifteen minutes for three additional

Dodds, and Noble<sup>7</sup> reported that esthynyl estradiol and diethylstilbestrol causes an inhibition of implantation and interruption of established pregnancy in rats and rabbits. They stated: "Everything we know about the primates suggests that its hormone control is the same as in lower animals, and it is extremely probable that the factors governing the implantation of the fertilized egg are fundamentally similar in women and in lower animals. The experimental conclusions arrived at above should thus be applicable to women, though the fact that very large amounts of estrogen are excreted by pregnant women makes it likely that the period during which estrogen treatment might be effective would be relatively much shorter than in rabbits." Van Wagenen and Jenkins<sup>8</sup> injected a series of 35 pregnant monkeys and reported that no abortion was initiated by the administration of estrogens in varying daily amounts up to 250 mg. with the highest total dosage of 1 gram. Moreover, they concluded that the interruption of pregnancy could not be initiated by a withdrawal of treatment with large doses of estrogens. They used diethylstilbestrol and estradiol dipropionate, theelin and estrone. They assumed that pregnant monkeys, receiving exogenous estrogens in the amounts cited, are able to accommodate themselves both to the drug and to its withdrawal. The only demonstrable effects of the drug were the accentuation of those physical changes normally initiated by estrogen in a normal pregnancy. Jeffcoate<sup>9</sup> reports that by prolonged administration of any type of estrogenic substance, the human uterus becomes sufficiently active to expel its contents. He used estrogen to increase the sensitivity and activity of the uterine muscle in missed abortion or missed labor. Smith, Smith, and Hurwitz<sup>10</sup> have reported the use of diethylstilbestrol in treatment of late toxemia of pregnancy with gratifying results. They reported no untoward effects resulting from the administration during pregnancy. Kellogg<sup>11</sup> reported the use of diethylstilbestrol in late accidents of pregnancy, and recommended it in the treatment of threatened and habitual abortion and premature labor. White<sup>12</sup> reported the use of diethylstilbestrol in 181 cases with no ill effect on pregnancy. She reported that the best and most economical hormones in use to date are diethylstilbestrol given by mouth and progesterone given intramuscularly. The average daily dose of each was 15 milligrams. Kurzrok<sup>13</sup> reported the use of estrogen in 42 habitual abortion cases. Thirty-nine (92 per cent) of these were delivered at term of normal living babies. He used 0.1 mg. of alpha-estradiol and 0.24 mg. of estriol daily by mouth. The author<sup>14</sup> in 1941 reported the use of diethylstilbestrol in the treatment of threatened and habitual abortion and premature labor. At that time no harmful effects were observed from the use of this hormone.

### Materials and Methods

Thirty-five women, proved to be from two weeks to seven months pregnant by the use of the Aschheim-Zondek test, were studied. Each received 100 to 250 mg. of diethylstilbestrol almost daily by mouth and intramuscularly from the second week of pregnancy until term. Total dosages ranged from 789.47 to 24,050 mg. of diethylstilbestrol.

In some instances the patients voluntarily discontinued the drug or failed to return to the Menstrual Disorder Clinic, but did return to be delivered, after taking 1,000 to 22,500 mg. of diethylstilbestrol. The sudden withdrawal of diethylstilbestrol did not produce any untoward changes or symptoms, regardless of the dose already taken.

All babies in this study were found to be entirely normal. They all exhibited a darkening of the areolae around their nipples, labia, and linea albae, similar in intensity to that of their mothers, indicating that this effect of diethylstilbestrol also is shared by the fetus. The diethylstilbestrol in doses of 100.0 to 1,000 mg.

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exposures. The uterus throughout the series failed to show any evidence of contraction, and remained the same size as on the control film.

Another patient was given 150.0 mg. of stilbestrol almost every other day, beginning 8 days before the expected date of confinement. She was due on June 5. Fourteen days after that date she had had no labor pains, having received 750.0 mg. of stilbestrol. The stilbestrol was stopped and she began to have labor pains in about thirty-six hours. One hundred fifty more milligrams of stilbestrol were given intramuscularly as soon as the pains started and every day for five days. The labor pains stopped within fifteen minutes. The patient was again given 100.0 mg. of stilbestrol daily by mouth from June 11 through June 25. At about 2:55 A.M., on June 26 she delivered a boy weighing 8 pounds  $2\frac{3}{4}$  ounces. Her labor was normal, lasting about eighteen hours. Microscopic sections of the cord and placenta were reported normal. Pregnancy apparently had been prolonged in this case for twenty-one days.

This patient was carefully watched and the following blood chemical studies were done: cholesterol, chlorides, uric acid, calcium, phosphate, and glucose tolerance tests. Frequent complete blood counts and urine analyses were performed.

### Discussion

This study was made in order to ascertain the effect upon the pregnant uterus of the administration and withdrawal of exogenous estrogen with regard to the continuity of pregnancy. Of primary interest was the effect of the drug upon the muscle of the uterus, the chief motive organ in the termination of pregnancy. The effect of exogenous estrogen on the mobility of the pregnant uterus with regard to the induction of premature labor was also examined in detail.

In the first series of 35 pregnant women, diethylstilbestrol was given by mouth in tablet form and intramuscularly in oil. The drug, being new, was given very cautiously at first. However, when these patients did not develop any signs or symptoms of toxicity and were normal as regards complete laboratory studies upon them, larger and larger doses were given until the total dosage ranged from 789.47 to 24,050 milligrams. In no instance was pregnancy interrupted during the administration or following the withdrawal of the stilbestrol. The sudden withdrawal of such large unphysiologic doses of exogenous estrogens did not cause any untoward effect on the pregnancies regardless of the time of pregnancy that the drug was withdrawn. The only abnormal symptoms occurred in patients who were given 500 or more milligrams as the initial dose. They became nauseated and vomited just like nonpregnant patients who had received 5 or more milligrams. The areolae of the nipples, midline of the abdomen, labiae, and especially the skin around the anus, became dark.

### Summary

Thirty-five pregnant women receiving daily doses of estrogens in amounts varying from 789.47 mg. to 24,050 mg. were observed for any unusual signs or symptoms.

In no case was abortion caused by the administration of stilbestrol, nor could it be associated with the withdrawal of the synthetic hormone.

TABLE I. COMPARATIVE ACCURACY OF OVARIAN HYPEREMIA PREGNANCY TEST WHEN TWO OR THREE RATS ARE USED PER TEST

TYPE OF URINE	NO. TESTS	FALSE POSITIVES	FALSE NEGATIVES	PER CENT CORRECT
Normal, childbearing age, pregnancy suspected, 2 rats	108*	0	17	84.5
Normal, childbearing age, pregnancy suspected, 3 rats	84†	0	8	90.5
Castrate, menopausal, normal at time of expected ovulation, 3 rats	14	1	0	92.9

\*96 later proved to be pregnant and 12 not pregnant.

†74 later proved to be pregnant and 10 not pregnant.

rat tests. Seventy-two of these urines were from pregnant and 10 were from nonpregnant women. Again, all errors were false negatives.

In 80 of the three-rat tests, one animal was injected by each of the three methods described above. It was hoped that the combination of intraperitoneal and subcutaneous injections would increase sensitivity, since a total of 3.5 ml. of urine was injected by this method. It was further planned to compare the two-hour intraperitoneal and six-hour subcutaneous techniques. As can be seen in Table II, no one of the three methods of injection proved to be significantly

TABLE II. COMPARISON OF THREE INJECTION METHODS IN THE OVARIAN HYPEREMIA PREGNANCY TEST

TEST PROCEDURE	NO. RATS AND URINES*	PER CENT CORRECT
1.5 ml. intraperitoneally and autopsy 2 hr. later	80†	63.7
2 ml. subcutaneously and autopsy 6 hr. later	80	61.4
Combination of above methods	80	63.7

\*On each urine 3 rats were used, one for each injection procedure.

†72 later proved to be pregnant and 8 not pregnant.

better than the others. The intraperitoneal method gave 49 out of 80 correct responses, and the subcutaneous and combination methods each gave 51 out of 80 correct responses. These results (61.4 to 63.7 per cent) also give a measure of the accuracy to be expected if only one rat is used for each urine.

Since tests here showed that pituitary gonadotrophin produces ovarian hyperemia, and since Farris<sup>4</sup> reported many false positives on nonpregnant women, a number of urines were tested from women under circumstances favoring a high excretion of gonadotrophin. The results of 14 such cases are presented in Table I. Five of these included women bilaterally oophorectomized six to twelve months previously, three were postmenopausal, and six were healthy women at the time of expected ovulation. One urine of this last group from a 34-year-old woman on the fourteenth day of a twenty-eight-day menstrual cycle produced a positive response in one rat. A repetition at the same time in the next cycle was negative.

Frequently part of the animals injected with a given sample exhibited positive results and part negative, indicating individual animal variation to chorionic gonadotrophin. The results of an experiment performed to measure the degree of variation are recorded in Table III. Standard commercial chorionic gonadotrophin, purchased on the open market, was used. It can be seen that some rats gave a positive response to 10 international units per ml. and others a negative with five and six times that dosage. The limited series given the combination of intraperitoneal and subcutaneous injections showed similar variations in individual animal response; moreover, the combined injection did not increase sensitivity.

## AN EVALUATION OF THE PREGNANCY TEST BASED ON OVARIAN HYPEREMIA IN THE IMMATURE RAT

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IN 1942 Salmon, Geist, Salmon, and Frank<sup>1</sup> observed that a subcutaneous injection of chorionic gonadotrophin produced an ovarian hyperemia within six hours in the immature female rat. They suggested this as a test for pregnancy and assayed 110 urines, 78 from pregnant and 32 from nonpregnant women. There were no false positive reactions, and an over-all accuracy of 99 per cent was reported. In 1943 Kupperman, Greenblatt, and Noback<sup>2</sup> employed a variation of this test for pregnancy. Urine was injected intraperitoneally into immature female rats and the ovaries examined two hours later. On 86 urines, 48 from pregnant women, an accuracy of 97 per cent was reported. All urines from nonpregnant patients were diagnosed correctly. In both of the above series three rats were used on each test.

Others<sup>3-5</sup> are not in agreement as to the accuracy and validity of the test, but the methods and techniques employed were not uniform. The present work was planned to determine the usefulness of the ovarian hyperemia pregnancy test as a routine laboratory procedure. In addition, the relation of accuracy to route of injection, the number of animals per test, and individual animal variations were investigated.

### Methods and Results

Immature female rats of the Sprague-Dawley strain were used, and urine was injected without previous extraction or concentration. Three technical variations were employed: (a) intraperitoneal injection of 1.5 ml. of urine with autopsy two hours later, (b) subcutaneous injection of 2 ml. of urine with autopsy six hours later, and (c) combined subcutaneous and intraperitoneal injections; i.e., the initial subcutaneous dose of 2 ml. was followed in four hours by an intraperitoneal injection of 1.5 ml. with autopsy two hours after the second injection: rats were usually killed by stretching the neck in the following manner. Firm pressure was applied to the back of the neck while exerting traction on the tail. The ovaries were exposed and observed within five minutes after the animals were killed. A definite red color of even a single ovary was considered to be a positive reaction. Observations were made under daylight type fluorescent lights. Whenever possible, first morning urine samples were used, and in general those with specific gravity less than 1.012 rejected. In some instances an initially negative test was repeated and both results were included in the final computation.

Two rats were used for each urine in 108 tests employing either the intraperitoneal or subcutaneous method. Ninety-six urines were from pregnant women and 12 from nonpregnant women. As seen in Table I, a correct diagnosis was made in 84.5 per cent of the cases. All errors were in failure of a positive response on urine from a pregnant woman. There were no false positives.

In 84 tests using three rats per urine sample, a correct diagnosis was made in 90.5 per cent of the cases, an increased accuracy of 6 per cent over the two-

laboratory with another. The same thing is true with other pregnancy tests lacking in sensitivity. Foote and Jones,<sup>6</sup> using one South African frog (*Xenopus laevis*) per test, obtained an over-all accuracy of about 90 per cent with no false positives, but over 50 per cent of the cases studied were nonpregnant women. If one calculates their accuracy using only the urines from pregnant women, the test is correct in only 76 per cent of the tests. If the negative cases are omitted from calculation in the three-rat tests reported in this paper, a correct diagnosis was made in 86.5 per cent of the tests.

The excretion of chorionic gonadotrophin reaches a sharp peak at eight to twelve weeks, with a relatively low titer early and late in pregnancy. Therefore, the accuracy of any pregnancy test dependent on the presence of chorionic gonadotrophin will vary with the period of gestation. Urines from all stages of gestation were used in the three-rat series, but 85 per cent were from the first trimester of pregnancy. Twenty-seven per cent were from patients within fifty days from the first day of the last menstrual period. The earliest positive reaction was obtained thirty days from the first day of the last menstrual period, the latest positive during the tenth lunar month.

Based on data reported in this paper, the ovarian hyperemia pregnancy test is now employed in this laboratory only when a rapid diagnosis is desired or when a given urine sample has proved too toxic for intravenous injection in a rabbit. For each test, three rats are injected intraperitoneally and autopsied two hours later. A negative response is considered unreliable.

### Summary

The ovarian hyperemia pregnancy test was employed in a series of urines from women in whom pregnancy was suspected. In 108 tests, using two rats per sample of urine, an accuracy of 84.5 per cent was obtained, but in 84 tests using three rats per sample, an accuracy of 90.5 per cent was obtained. All errors were failures to get a positive reaction from urines of pregnant women.

With 14 additional urines collected when increased excretion of pituitary gonadotrophin might be expected (castrate, menopause, and at time of ovulation), one gave a positive reaction.

In 80 of the three-rat tests, one rat was injected intraperitoneally and autopsied two hours later, one was injected subcutaneously and autopsied six hours later, and one was given both types of injection. There was no significant difference in degree of accuracy by any of the three methods.

Individual animal variation in the ovarian hyperemia response was determined by injecting rats with a series of graded doses of chorionic gonadotrophin. The results showed an extreme variability in individual animals.

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TABLE III. OVARIAN HYPEREMIA RESPONSE TO VARYING AMOUNTS OF CHORIONIC GONADOTROPHIN\*

CONCENTRATION OF CHORIONIC GONADOTROPHIN (I.U. PER ML.)	RESPONSE TO 1.5 ML. I.P.	RESPONSE TO 1.5 ML. I.P. PLUS 2 ML. SUB. CUT.
3.3	00000	
6.6	00000	+0000
10	++000	
13.3	+++00	++000
16.6	++000	
20	++000	
23.3	+++00	+0000
26.6	++000	
33.3	++000	+++00
50	+++00	
66.6	+++00	+++00

o = Negative response

+ = Positive response

\*With each dosage level five animals were used. Therefore, each o or + represents response of an individual animal.

### Discussion

The results with the rat ovarian hyperemia pregnancy test do not agree with the optimistic reports from certain other investigators (Salmon and co-workers;<sup>1</sup> Kupperman and associates;<sup>2</sup> Kaminester<sup>3</sup>) but neither could the unpredictable results obtained by Farris<sup>4</sup> be confirmed. The test in the author's experience is not as accurate as the Asehheim-Zondek or Friedman. It does have the distinct advantage of rapidity, especially since the two-hour method is as accurate as the six-hour method. A negative response is difficult to interpret because of test insensitivity, but a positive response is always significant. Zondek, Sulman, and Black,<sup>5</sup> using subcutaneous injections, report the two-hour test as being less sensitive than the six-hour test, and both are reliable only when positive. They report an accuracy of 92.2 per cent in positive cases by the six-hour test. However, data presented here does not indicate any advantage of the six-hour over the two-hour test when in the latter the urine is injected intraperitoneally.

The method of killing rats by stretching the neck causes death almost instantly without struggling. Although different from ether or illuminating gas methods used by others, it is difficult to see how this could influence the end point of the test. In a few cases the animals were killed with carbon monoxide or ether, and the subjective impression was gained that the hyperemic response was unaffected.

The end point of this test is not sharp, and at first there is a tendency to avoid decision by reporting the results as questionable. Subsequently, all questionable reactions were considered negative, as it was believed advisable to sacrifice some over-all accuracy in order to have all errors in one predictable direction. In other words, an accuracy of 92 per cent with all errors false negatives was considered better than an accuracy of 96 per cent with both false negatives and false positives.

Since all errors will be expected with pregnant patients, the percentage accuracy of any series will increase when it contains large numbers of nonpregnant women. This must be taken into account when comparing results of one

one finger with difficulty. Two cervixes of equal size were visible and palpated. A small amount of sanguineous discharge was observed exuding from the left cervical canal. Histologic examination of the tissue which had been removed from the slightly dilated external os revealed the presence of chorionic villi, thereby confirming the diagnosis of incomplete abortion. The vaginal bleeding ceased following the administration of  $\frac{1}{320}$  grain of ergotrate every four hours for six doses.

In July, 1945, the patient returned to the prenatal clinic stating that her last menstrual period had begun on May 22, 1945. Examination revealed the presence of a pregnancy in the left uterus. She made regular routine visits to the clinic until November, at which time her husband was transferred to another military installation. The pregnancy had progressed uneventfully up to the time of the patient's departure from this clinic. Efforts to ascertain the ultimate outcome of this pregnancy have been unsuccessful.

An interesting observation relative to this case is that not only had there been failure of fusion of the Müllerian tract as manifested by duplication of the uterus, cervix, and vagina, but there also had been improper fusion elsewhere in the body; namely, the cleft palate and the harelip.

It is also interesting to note that each of the three pregnancies had been in the left uterus. This fact is readily understandable, on the basis of the right vagina being too small to permit coitus.

CASE 2.—A 23-year-old white nulligravida reported to the outpatient clinic of the hospital in June, 1943. Although she had been married but five months, she was considerably concerned about her failure to have conceived within this period of time. Examination revealed the presence of double vagina and double cervix. A hysterosalpingogram further disclosed duplication of the uterus. The past history had been negative for dysparennia, dysmenorrhea, or abnormalities of the menstrual flow.

The patient returned to the prenatal clinic on Dec. 2, 1943, with the history of amenorrhea since September 24. An intrauterine pregnancy of approximately ten weeks' duration was diagnosed. Confinement date was calculated as July 1, 1944.

The pregnancy progressed uneventfully until the membranes ruptured spontaneously at 8:00 A.M. June 22, 1944, followed by strong uterine contractions which recurred at four-minute intervals. Examination of the patient upon admission to the hospital at 9:30 A.M. revealed a full-term infant with vertex presenting and overriding the pelvic brim. Efforts to engage the head in the pelvis were unsuccessful. The cervix was found to be dilated one fingerbreadth. The failure of the vertex to descend into the pelvis was presumed to be on the basis of obstruction by the nonpregnant uterus. This assumption was confirmed when the patient was delivered by laparotrachelotomy. A living 5 pound, 5 ounce female infant was extracted from the right uterus. The enlarged, non-pregnant, left uterus presented as the dystocic factor.

The postoperative course was uneventful and the patient departed from the hospital on the eleventh day following operation. When she was examined six weeks later, involution was found to have progressed at a normal rate.

CASE 3.—A 25-year-old white para 0, gravida i made her first visit to the prenatal clinic on Sept. 22, 1944. She stated that her last menstrual period had begun on July 19, 1944. The past history revealed that she had been treated for hypoglandularism for several years by the oral administration of 3 grains of thyroid extract daily. The menses which had commenced at the age of 10 years recurred every twenty-eight days and lasted five to seven days. Duplication of the uterus, cervix, and vagina had been demonstrated by hystero-

## PREGNANCY COMPLICATED BY DOUBLE UTERUS, CERVIX, AND VAGINA

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THE management of pregnancy complicated by duplication of the generative tract presents a complex problem worthy of the most serious deliberation. The infrequency with which this clinical entity is encountered provides the obstetrician with little personal experience on which he may draw in determining the course to be followed in any individual case. Taylor<sup>1</sup> stated that even a specialist may see but a few cases of this deformity during a lifetime. Smith<sup>2</sup> estimated that the incidence of double uterus of some type, exclusive of simple septate vagina and uterus arcuatus, was 1 in 1500 pregnancies.

The recording of additional experiences with a relatively rare obstetric complication makes available further information which may aid in the selection of the proper procedure for management of similar cases. With this view in mind, three cases are reported in which pregnancy complicated by double uterus, cervix, and vagina was carried to a successful termination.

### Case Reports

CASE 1.—A 26-year-old, white, para 0, gravida i was admitted to the hospital on Oct. 14, 1943, with the complaint of abdominal cramps of ten to fifteen seconds' duration recurring every seven to eight minutes. The confinement date had been estimated as October 26. The past history was significant only in that the patient had had a plastic repair of a congenital harelip and cleft palate.

Gross physical examination of the patient disclosed no abnormalities. The uterus was found to contain a living, full-term fetus with vertex presenting. The blood pressure recordings were within normal limits. Urinalysis was negative for albumin. The red blood cell count and the hemoglobin determination revealed no evidence of anemia.

Following admission to the hospital the abdominal pains vanished, permitting the patient to sleep throughout the night. She complained of a backache and observed the passage of bright red blood and clots per vaginam upon awakening the following morning. The obstetrician in attendance at that time presumed the possible presence of placenta previa. After taking the usual precautions in such cases, he examined the patient vaginally. A double vagina and double cervix were palpated. Up to this time, neither the patient nor the physician had had prior knowledge of the presence of the anomaly. In view of the combination of the congenital abnormality of the generative tract and the bleeding from the placental site, delivery of the infant via the abdominal route was elected. On October 15, a living 6 pound, 12 ounce female infant was delivered from the left uterus by classical cesarean section. The postoperative course progressed without untoward event.

The patient was seen by the writer for the first time on March 30, 1945, when she stated that she had had vaginal bleeding for three days. The last regular menstrual period had commenced on Feb. 13, 1945. Examination disclosed a thick septum which extended throughout the entire length of the vagina, dividing it into a large left compartment and a smaller right portion that admitted

# BACTERIOLOGY OF VAGINA IN TOTAL HYSTERECTOMY

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FOR many years at the Free Hospital for Women the policy has been to change gloves and instruments after the completion of a total hysterectomy before removing the appendix and closing the abdominal wall. With the current trend toward total hysterectomy in preference to subtotal, the procedure of changing gloves and instruments caused considerable loss of time as well as extra work for the already hard-pressed operating room staff. It was thought that it would be interesting and instructive to find out just what organisms might be found in the upper vagina in these cases.

Preparation of the vagina preoperatively varies in nearly every clinic and hospital in the country. This would indicate that no specific procedure or preparation has been found that is acceptable in all cases. At the Free Hospital for Women, the preoperative vaginal preparation has been markedly changed in the past few years. Preoperative douches which were previously given the night before and the morning of operation have been discontinued. The surgeon before anesthetic examination of the pelvis thoroughly wipes out the vagina with a dry sponge, and then adequately swabs it with tincture of Zephiran. The pelvic examination is then done and the operative vaginal procedure indicated is carried out. Finally, the vagina is well cleaned of any debris, and tincture of Zephiran is again generously applied to the mucosa, many of the operators electing to leave a dram or two in the vagina before proceeding with the abdominal procedure.

This report is based on the findings in 133 consecutive total hysterectomies from both the Free and Private divisions of the Free Hospital for Women. The smear reports in this group showed 90 negative and 43 positive. Of the 43 positive smears (Table I) 20 were gram positive cocci, four were gram negative cocci, and twenty were gram negative bacilli.

The culture reports were negative in 87 cases and positive in 46. The organisms cultured are shown in Table II.

The clinical course in this series of cases was uneventful in 124 patients. The remaining nine were listed as having complications, none of which were of any serious moment.

Three patients had postoperative distention sufficient to be placed on constant suction for twenty-four hours.

TABLE I. SMEAR REPORT

NEGATIVE—90		POSITIVE—43	
		Gram positive cocci	20
		Gram negative cocci	4
		Gram negative bacilli	20

TABLE II. CULTURE REPORT

NEGATIVE—87		POSITIVE—46	
		Staph. albus	19
		Microcatharalis	5
		Enterococci	9
		B. coli	29
		Hemolytic staph. aureus	1



salpingography during a previous investigation of sterility of three and one-half years' duration.

The patient was 5 feet, 3 inches tall and normally weighed 237 pounds. There was marked obesity of the abdomen, thighs, and the upper extremities. Vaginal examination disclosed division of the vagina into two compartments of relatively equal size by a thick septum which extended throughout its entire length. Both cervices were palpated and visualized. The extreme obesity of the patient, the high symphysis, and the acute angle of the pubic arch combined to make a detailed study of the uteri impractical, due to the severe discomfort experienced by the patient when it was attempted. It was determined, however, that a six weeks' intrauterine gestation existed, though no differentiation was feasible as to which uterus was the site of the pregnancy. Confinement date was estimated as April 26, 1945.

The pregnancy progressed normally. Roentgenographic study on March 23, 1945, disclosed a single fetus with breech presenting. An android type of pelvis with slightly convergent side walls was also demonstrated.

The physical and endocrine make-up of the patient was such that the advent of the adipose-dystrophy-dystocia syndrome during labor might well be anticipated. This factor, coupled with that of a breech presentation in the presence of duplication of the generative tract, presented sufficient evidence to warrant delivery of the infant by elective cesarean section. On April 18, 1945, a living 7 pound, 6 ounce female infant was delivered from the right uterus by laparotrachelotomy under local anesthesia. Inspection of the pelvis revealed that the nonpregnant uterus would not have been an obstructing factor in the event of vaginal delivery. The patient departed from the hospital in excellent condition on the ninth postoperative day. Involution was found to be progressing normally when she was examined six weeks after operation.

### Summary

Three cases are reported in which pregnancy complicated by double uterus, cervix, and vagina was carried to a successful termination. The determining factor in the obstetric management of each case was not the congenital anomaly, but the advent of such complications which of themselves necessitated operative intervention.

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## PLACENTA ACCRETA FOUND AT CESAREAN SECTION FOR PLACENTA PREVIA, WITH PRESERVATION OF THE UTERUS\*

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**P**LACENTA accreta is an uncommon complication of the third stage of labor. The incidence of this condition varies widely in the literature from a low of one in 40,000 cases<sup>1</sup> to one in 1,956 cases, as reported by Irving and Hertig.<sup>2</sup>

The exact incidence of placenta accreta accompanying placenta previa is not known. Wilens,<sup>3</sup> in 1942, reviewed the literature, and could find only two cases of placenta accreta found at cesarean section for placenta previa, and he added a third case. Jackson,<sup>4</sup> reporting a similar case in 1943, reviewed the case histories of the London Hospital and found four other cases of placenta previa and accreta. He further stated that there were about fifteen such cases reported in the world literature. In 1944, Shotten and Taylor<sup>5</sup> reported a case of complete placenta previa-accreta occurring in a primigravida.

### Case Report

Mrs. A. M., 35-year-old gravida ii, was first seen in May, 1945. Her last menstrual period was March 11, 1945; her estimated date of delivery was Dec. 18, 1945. Examination at that time was essentially normal, and pelvic measurements were noted as adequate.

Her past obstetric history revealed that her first pregnancy in June, 1941, was complicated by retained placenta necessitating manual removal. The patient subsequently returned to the hospital one month later for curettage because of persistent bleeding.

Present pregnancy progressed normally until Jan. 2, 1946, two weeks past the expected date of delivery. At this time, the patient noticed painless vaginal bleeding, and was hospitalized immediately. Since placenta previa was suspected, the patient was typed and cross-matched for transfusion.

Vaginal examination was done, revealing the cervix to be dilated 4 cm., membranes intact, and with about one-half of the left posterolateral wall of the cervix covered by placenta. The infant was a breech presentation in right sacroposterior position.

Since brisk bleeding occurred during examination, an immediate low cervical cesarean section was done, and a normal living male infant weighing 9 lbs., 15 oz. was delivered by breech extraction.

The patient received intravenous ergotrate, but there was no evidence of spontaneous separation, and manual removal of the placenta was attempted. That portion covering the lateral posterior aspect of the cervix and lower uterine segment separated easily, but at about the equator of the placenta the cleavage plane disappeared; the entire superior half of the placenta was intimately attached to the uterine wall. Hysterectomy was considered, but in view of the excellent condition of the patient and her desire for more children, an attempt was made to remove the placenta by sharp and blunt dissection. This was carried out with considerable difficulty, but without perforating the uterine wall. Bleeding was moderate and was controlled by firm pressure with hot

TABLE III. CLINICAL COURSE

UNEVENTFUL—124	COMPLICATIONS—9
	Postoperative bleeding 1
	Dicoumarol—fifth day
	Increased prothrombin time
	Low grade pelvic sepsis 1
	Negative smear and culture
	Postoperative abdominal wound 1
	hematoma
	Phlebitis 1
	Pyelitis 1
	Sulfadiazine idiosyncrasy 1
	Postoperative distention 3
	Constant suction

The postoperative treatment of these cases naturally varied with the individual operator. The majority of these patients were ambulatory by the fifth day. No difficulties could be ascribed to early activity, and the majority of the patients seemed to respond favorably to early ambulation. The average hospital stay in this series was 11.68 days.

The use of intraperitoneal sulfonamide in this series was considered. No sulfonamide was used in 92 cases, and in 41 cases varying amounts, averaging two and one-half grams of either sulfanilamide or sulfathiazole powder dusted about the pelvis. One might expect that sulfonamides were used in the cases that suggested potential difficulties. This, however, was not so. Sulfonamides were used in all cases by some men, and not at all by the majority of the staff. The clinical course of those women who received sulfonamides was no different from those in the nonsulfonamide group. It must be remembered that the type of pathology encountered at the Free Hospital may well be termed "clean gynecology," there being very few operative efforts on acute pelvic infections. The pathologic study as shown in Table IV clearly confirms this statement.

TABLE IV. PATHOLOGIC DIAGNOSES

Fibroids	58
Pelvic inflammatory disease	22
Chronic cervicitis	17
Adenomyosis	14
Endometriosis	13
Ovarian cyst	10
Endometrial polyps	4
Dysfunctional bleeding	3
Carcinoma in situ	3
Carcinoma of endometrium	3
Carcinoma of cervix (early)	1
Placental polyp	1
Ectopic pregnancy	1
Prolapse	12

### Summary

1. Infection from the vagina after adequate preparation is almost negligible in cases of total hysterectomy.
2. The use of sulfonamides are of little or no value in the usual case.
3. Adequate hemostasis with elimination of "puddling" seems to be most necessary to insure a smooth postoperative course.
4. A definite sense of security has been obtained from this study.

The writer is indebted to the members of the Staff of the Free Hospital for Women for their courtesy in obtaining material from their private cases for this study.

All the bacteriological work was done by Miss Olga DeSimone of the Hospital Laboratory Staff.

We realize that no conclusions can be drawn from one or two such cases, but it appears that where the desire for future pregnancies is great, a more conservative method of treatment can be attempted; but only in the rare case when placenta accreta is accidentally found at cesarean section where the separation can be made under direct vision.

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sponges and by another ampule of intravenous ergotrate. The uterus was then packed firmly with plain gauze and a DeLee shuttle passed into the vagina. The uterus was closed in the usual fashion and the abdominal wall in layers.

The patient received 500 c.c. of whole blood and 1,000 c.c. of fluids at termination of the operation. The pack was removed in twenty-four hours with normal bleeding. The patient daily received 200,000 units of penicillin prophylactically for the first four postoperative days. The day following operation the temperature reached 100.2° F., and then rapidly fell to normal. The remainder of her hospital stay was uneventful, and she was discharged with her infant on the eleventh postoperative day.

*Pathologic Report* (Dr. Martha E. Madsen).—

*Gross:* The placenta measured 37 by 20 by 8 cm. A large portion measuring 23 by 17 cm., showed complete flattening of the cotyledons and replacement by hyaline, fibrous, almost cartilaginous material. The cord was located approximately in the center of this region. The rest of the placenta presented fairly well-preserved, bloody cotyledons.

*Microscopic examination:* The decidua basalis was represented merely by an occasional group of cells of the compact layer. No glands were found. Attached directly to the muscularis in many areas was an irregular layer of collagen-like material showing some hyaline and granular degeneration, containing cells singly and in groups which took a deep stain. Many were multinucleated, having a trophoblastic appearance. In the other areas, the placental villi rested directly on the muscularis. The sections containing muscle showed the latter, and only a thin layer of poorly preserved muscle was present. In many sections were seen areas of fibrosis in the muscularis.

*Diagnosis:* Placenta accreta, almost complete.

### Comment

Placenta accreta is defined by Aaberg and Reid<sup>6</sup> as the coherence of the placenta to the myometrium, resulting from the absence of the decidua basalis, particularly of the stratum spongiosum, with either direct contiguity to, or invasion of the myometrium by chorionic villi, or by the myometrial invasion of the placental septa. They further classify this condition into: complete, when all the cotyledons are involved; partial, when one or several cotyledons are involved; and focal, when part of a single cotyledon is involved.

The etiology of this condition presupposes failure of an adequate decidual reaction. It usually follows some disease or injury to the decidua. The majority of the reported cases occur in multigravida, and were preceded either by a vigorous curettage, manual removal of the placenta, or a previous cesarean section. In the case reported by Shotten and Taylor<sup>5</sup> the patient, a primigravida, had been treated for infertility and had both tubal insufflation and a diagnostic curettage.

The usual and accepted treatment for this condition is hysterectomy. Phaneuf,<sup>1</sup> in 1933, in a review of 82 collected cases, showed unquestionably that immediate hysterectomy is the treatment of choice. Potter,<sup>7</sup> however, reported a case in which he allowed the placenta to remain within the uterus; the patient had a stormy course, but made a complete recovery. Similar cases have been recorded.

Wilens<sup>3</sup> case was treated very similarly to ours, and both patients made good recoveries.

The following case was a tubal pregnancy that had recently emerged into a secondary abdominal pregnancy, and we believe was capable of developing into a more advanced form of secondary abdominal pregnancy if it had not been intercepted surgically.

H. W., a Negro gravida ii, para 0 aged 33 years, was admitted to the Cook County Hospital on Dec. 26, 1945. Her last menstrual period occurred on Oct. 23, 1945. Her chief complaints at the time of admission were persistent nausea developing into severe attacks of vomiting for the past few days, coupled with cramp-like pains in the lower half of the abdomen. The latter symptoms had been present for one month with some vaginal spotting. Since her last menstrual period there had been some loss of weight, the exact amount was unknown. Concerning her past history, the patient had one previous spontaneous three months' abortion. The initial examination of the patient revealed that she was dehydrated. There was pain and tenderness of the lower abdomen but no vaginal bleeding. The conjunctivae were pale, her blood pressure was 110 systolic and 80 diastolic, and the pulse rate was 90 per minute. The blood examination showed 3,250,000 red cells, 80 per cent hemoglobin, and 8,500 leucocytes. The urine contained a heavy trace of acetone.

The impression at this time was that we were dealing with a hyperemesis gravidarum and a threatened abortion. A pelvic examination was, therefore, deferred. During the next five days wherein she had complete bed rest, parenteral fluids administered and sedation, the vomiting, cramps, and spotting ceased. A vaginal examination revealed a nonmovable cystic mass the size of a grapefruit, to the right and posterior to a normal-sized uterus. The Aschheim-Zondek test was positive. With a diagnosis of extrauterine pregnancy, possibly abdominal in type, an exploratory laparotomy was performed. There was a small amount of free blood present, the uterus was slightly enlarged, soft, and was pushed to the left and against the bladder. The right tube was definitely enlarged, thickened, and had the shape of a retort. At the distal end there was a cysticlike structure, the size of a grapefruit. The mass was bound down to the posterior aspect of the uterus and to the right broad ligament. The proximal part of the left broad ligament was also attached to it. The right tube and what had emerged from it was carefully dissected from its bed, and thus a specimen was obtained; it revealed a fetus within its amniotic sac and protruding through the fimbrial ring. The appearance of this specimen resembled a staghorn-shaped tube. The latter was opened and a three-month fetus (Fig. 1) was seen still attached to the tubal lumen by a thin cord. The patient made an uneventful postoperative recovery.

A study of this case and specimen gave us the rare opportunity of seeing a secondary abdominal pregnancy that had very recently emerged from its status as a primary tubal gestation.

25 E. WASHINGTON STREET

## EARLY FORM OF SECONDARY ABDOMINAL PREGNANCY\*

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A TUBAL pregnancy developing in the ampulla may be extruded into the peritoneal cavity. If further development ceases with this extrusion, it is known as tubal abortion, a frequent termination. If, however, the ovum continues to grow outside of, but maintains its connection to within the tube, it develops secondarily into an abdominal pregnancy. Such a possibility is rare, and is more likely to evolve when a pregnancy in the ampullar portion



Fig. 1.

of the tube is implanted in the more distal part of the oviduct such as in the vicinity of fimbria ovarica. The extruding fetus emerging through the fimbrial ring of the tube becomes adherent to all contiguous tissue. At first these adhesions are more likely to be with the posterior aspect of the broad ligament and the uterus. In the more advanced abdominal pregnancy the adhesions are more extensive, involving the gastrointestinal tract or any part of the peritoneal cavity. At or about the time of maturity of the fetus the patient has spurious labor pains, and, if the fetus is not removed at that time, it dies. A fifteen-month fetus was reported by one of us (A.J.K.) in 1942.

\*Presented before the Chicago Gynecological Society, March 15, 1946.

## PREGNANCY AND SICKLE-CELL ANEMIA

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THIS disease was discovered in 1904 by Dresbach, and Herriek described the acute phase in 1910. The name "sickle-cell anemia" was applied to the anemic phase and the term "sicklemia" used to designate the asymptomatic sickle-cell trait. Both are congenital, hereditary blood dyscrasias, transmitted to either sex as a dominant Mendelian factor. Sickle-cell anemia is confined almost exclusively to the Negro, although Killingsworth and Wallace reported a case of sickling in the Mexican, and Fowler mentions that it has been seen in the white race. Seven to 8 per cent of the Negro race possesses a sickle-cell trait, but only 0.8 to 1.0 per cent develops true sickle-cell anemia. It is readily seen that pregnancy associated with sickle-cell anemia is a rare entity. In addition, only a few women with the disease become pregnant, although the reason for infertility is unknown.

The majority of patients with sickle-cell anemia are young, and the life expectancy is short because of intercurrent infection. In fact, most hospital admissions are motivated by acute infection. There is also an unexplained tendency to thrombosis.

Gestation seems to exert an unfavorable influence, but with proper supervision, including frequent blood transfusion, patients can be carried to term. Toxemia seems to be more frequent than normal expectancy. One third of the reported cases died during pregnancy, labor, or the puerperium (Kobak). There seems to be a tendency to abortion, premature labor, and stillbirth. Postpartum patients are prone to develop sepsis. The sickling phenomenon was present in one third of the babies.

So few reports (18 cases)<sup>1-6</sup> of pregnancy and sickle-cell anemia are available that it is difficult to prognosticate the outcome of an associated pregnancy. Therefore, there is justification to report individual cases as they occur. One of the two under consideration is of interest because of a five-year period of observation of both mother and child.

CASE 1.—K. B. G., 11891, a Negro woman, aged 18 years, gravida i, para 0, was first seen at Baylor University Hospital (Dallas) on January 6, 1941. The menses were normal, and the last menstrual period was September 18, 1940, making the expected date of delivery June 25, 1941. Weakness, dyspnea on exertion, pain in the right side and back, lack of appetite, constipation, and nocturia appeared Dec. 1, 1940, and thereafter gradually increased in severity.

The blood pressure was 142/76. There were 6.1 Gm. of hemoglobin per 100 cubic centimeters. The red cell count was 1,480,000, and the total white cell count was 21,000, with a normal distribution of cells. The icterus index was 12.7. Urinalysis revealed 10 mg. of albumin per liter of urine and many white blood cells, some of them clumped. The patient did not have syphilis. A tentative diagnosis of anemia complicated by pregnancy was made. Three hundred twenty milligrams of ferrous sulfate three times daily, and bed rest were prescribed.



## MEIGS' SYNDROME IN THECA-CELL TUMOR OF THE OVARY\*

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THE association of abdominal ascites, hydrothorax, and an ovarian tumor has been recognized for years, but it was not until 1937 that Meigs and Cass emphasized its clinical importance and it became an established syndrome.

The patient, a white married woman, aged 44 years, was admitted to the chest service of the Michael Reese Hospital on March 2, 1946. She complained of dyspnea on slight exertion for the past two months, and the presence of an abdominal mass which she had noticed for a similar length of time. Her past history was irrelevant, except for a hysterectomy in 1938 and influenza in December, 1945.

On March 4, 1946, 900 c.c. of a clear, straw-colored fluid were removed from the right pleural cavity. Gynecologic consultation on March 5, 1946, revealed the following findings: cervical polyp and a grapefruit-size mass in the left lower quadrant. The diagnosis of fibroma of the left ovary with hydrothorax (Meigs' syndrome) was made.

The right chest cavity was tapped, as shown below:

March 4—	900 c.c. clear fluid
March 6—	2,000 c.c. clear fluid
March 7—	300 c.c. clear fluid
March 9—	900 c.c. clear fluid
March 14—	830 c.c. clear fluid
<hr/>	
Total—	4,930 c.c. clear fluid

Her condition was such that she could now be subjected to laparotomy, which was done on March 16, 1946. The findings were moderate ascites, multiple adhesions presumably from the previous laparotomy, and a large tumor of the left ovary which grossly appeared to be malignant. Both tubes, ovaries, and the remaining portion of the uterus were removed. The patient made an uneventful postoperative recovery, with the exception of a moderate degree of ileus.

The pathologic report was theca-cell tumor of the left ovary with degenerative changes and multiple simple cysts.

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\*Presented at a meeting of the Chicago Gynecological Society, May 17, 1946.

there were 15,142 deliveries, with 5,325 in Negro women. This represents an incidence of approximately 1:5,000 among the Negro clientele.

CASE 2.—R. L., W13964, a Negro woman aged 16 years, gravida i, para 0, was seen in the prenatal clinic on April 5, 1944, complaining of amenorrhea for eight months and nausea, vomiting, fainting spells, and visual disturbances for three months. There were no abnormal physical findings, and the blood Wassermann was negative. She entered the hospital in labor on July 1, 1944, with a normal blood pressure (100/62), and was delivered spontaneously of a normal female infant weighing 3,030 Gm., after eight and one-half hours of labor. On admission the red cell count was 2,780,000, the hemoglobin was 8.5 Gm., and the white cell count was 9,700. A moist preparation of red cells revealed 85 per cent sickle cells.

The mother and baby had an uneventful puerperal course and were discharged on the seventh day. They were seen again in March, 1946, at which time the mother complained of pain in the right upper quadrant and irregular menstrual periods. Her child was almost two years of age and apparently in good health. Moist preparations of red cells showed 55 per cent sickling in the mother, and 15 per cent in the child.

These patients represent cases number 19 and 20 to be reported. Both patients were young, in their teens, carried to term, and normal infants were obtained. In neither instance was there toxemia. The former received ten liters of whole blood ante and post partum. No permanent ill effects from transfusion resulted, although some of them were followed by acute abdominal crises. Sickle-cell anemia was diagnosed early in pregnancy in the first patient and during labor in the latter. Both infants inherited the sickling trait. There was absence of severe puerperal infection in both women. Neither has been able to become pregnant since, although no contraceptives have been used.

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On Feb. 17, 1941, the patient was admitted for diagnosis of the type of anemia and further therapy. The blood pressure was 130/70 millimeters of mercury, the temperature was 99° F., and the pulse and respiratory rates were 100 and 20 per minute, respectively. There were several tender sears on the legs, but no lymph nodes were palpable. The mucous membranes were pale, the lips were dry and fissured at the angles of the mouth. There was a loud systolic murmur over the mitral area, probably due to the anemia. The blood and hemoglobin values remained essentially unchanged. The mean corpuscular volume, hemoglobin, and concentration were 115, 28, and 25 millimicrons, respectively. The fragility test showed complete hemolysis at a saline concentration of 0.24. The reticulocyte count was 18.8 per cent, and the icterus index 19. There were 1,260 mg. of urobilinogen per 100 grams of feces. Urinalysis revealed 100 milligrams albumin per liter of urine. A moist preparation of red cells showed sickling.

The patient received 2,500 c.c. of whole blood, and was discharged eleven days after admission, with a hemoglobin of 10.2 Gm. and a red cell count of 3,000,000.

During the next month and a half, weekly transfusions of 500 c.c. of whole blood were given, and occasionally were followed by acute abdominal crises. The hemoglobin varied between 9 and 10 Gm., and the red cell count remained near 3,000,000. On April 25, 1941, a red cell count of 2,500,000 reticulocyte count of 25 per cent, icterus index of 31, and moist preparation showing sickling of all the red cells motivated another admission to the hospital. The patient again remained under observation for eleven days, during which time 1,500 c.c. of whole blood were given. On the day of discharge, the hemoglobin was 8.8 Gm., and the red cell count 3,000,000.

On June 1, 1941, the patient fell into false labor, but three days later definite labor began and was terminated after sixteen hours by the spontaneous birth of a normal male infant weighing 3,200 grams. The estimated blood loss at labor was 500 cubic centimeters. During this admission, prior to the onset of true labor, the hemoglobin was 7.5 Gm., and the red cell count was 2,710,000, with 10 per cent sickling of the red cells. Six transfusions, one antepartum and five postpartum, each of 500 c.c. of whole blood were given.

For three days following delivery the temperature ranged between 102° and 104° F., and thereafter was normal. The patient was discharged on the fourteenth postpartum day, with a hemoglobin of 10.0 Gm. and a red cell count of 3,030,000.

One per cent of the red cells from the umbilical cord showed sickling. Later, red cells of the infant showed 2 to 5 per cent sickling, but on the day of discharge only an occasional red cell showed this tendency. At time of discharge the child weighed 3,100 grams.

Six weeks after delivery the maternal hemoglobin was 12.2 Gm., the red cell count was 3,640,000 and 1 per cent of the cells showed sickling. Seven months after delivery the hemoglobin was 6.1 Gm., and the red cell count was 2,000,000, with 90 per cent sickling.

The patient was seen again in March, 1946, and still complained of weakness on exertion, cramping of muscles, and occasionally abdominal pains. There had been no subsequent pregnancies. At this time the hemoglobin was 7.5 Gm., red cell count 1,740,000, and a moist preparation of the red cells showed 100 per cent sickle cells. The child was almost five years old and appeared to be well. A moist preparation of his red cells also showed 100 per cent sickle cells. The hemoglobin was 10.5 Gm., and the red cell count was 4,320,000.

Only one case of sickle-cell anemia associated with pregnancy was seen at Parkland Hospital during the ten-year period from 1935 to 1945, although

Fig. 1.



Fig. 2.

Fig. 1.—Section of tumor from perineum showing a benign fibroadenoma. Ducts and acini are embedded in a liberal stroma ( $\times 120$ ).  
Fig. 2.—Tumor from perineum. Note benign hyperplasia of epithelium and stroma ( $\times 230$ ).

## FIBROADENOMA OF SUPERNUMERARY MAMMARY GLAND TISSUE IN VULVA

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ON REVIEWING the literature concerning supernumerary breasts during the last fifteen years, one finds that this abnormality is of relatively frequent occurrence. However, the location of supernumerary breast tissue in some part of the vulva is rare, and very few cases of such have been reported. De Cholnoky<sup>1</sup> has reviewed the literature on this subject up to 1939, and more recently Weinshel and Demakopoulos<sup>2</sup> have brought a review of the subject up to date.

### Report of Case

An unmarried, 47-year-old schoolteacher sought advice because of menorrhagia and because she thought she had an abdominal tumor. Otherwise she was well; her past history was noncontributory. In the course of a physical examination it was discovered that she had uterine fibroids and a lump on the right side of the perineum. The lump was nontender, situated just under the skin, was firm, and freely movable. The patient did not remember when she first noticed it, but she had been aware of its presence "for years." It had caused her no inconvenience. Its size had remained stationary for a long time.

On July 27, 1945, a hysterectomy was performed, and at the same time the lump in the perineum was excised. It was encapsulated and "shelled out" of the tissue without difficulty. The patient made an uneventful recovery.

*Pathologic Report.*—The mass measured 3.0 by 2.0 by 1.3 cm. It was encapsulated and its external surface was gently lobulated. It felt firm and elastic. The cut surface was uniformly grayish-white and solid.

Microscopic sections showed well-developed breast tissue presenting the pattern of growth of a pericanalicular fibroadenoma. It was composed of ducts and acini surrounded by zones of pale-staining, loosely arranged fibrous connective tissue (Figs. 1 and 2). The ducts were not dilated or distorted. Some of the acini contained a small quantity of an eosin-staining substance, but in general they showed no secretory activity or undue hyperplasia. The glandular tissue was supported by a rather liberal amount of compact collagenous fibrous connective tissue. The tumor was definitely benign in character.

### Discussion

From the embryologic viewpoint, supernumerary breasts may be found at any point along the mammary ridge or "milk line" which runs from the axilla through the lateral border of the pubic region to end on the upper medial surface of the thigh. Consequently, the presence of breast tissue in some part of the vulva is explainable on this developmental basis. Nevertheless, judging from the number of recorded cases<sup>3-7</sup> this abnormality is rarely encountered in the vulva.

## DICHORIAL UNILATERAL TUBAL TWINS

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THE recorded cases of tubal twins have been critically reviewed by Arey<sup>1</sup> in 1923, and again in 1938 by Falk and Bliniek.<sup>2</sup> The latter authors accepted 65 cases, and reported two of their own. Since this report 11 additional cases<sup>3-12</sup> have been added to the literature, bringing the present total to 78. These are all of the single ovum type, as indicated by similarity of the size and developmental age of the embryos or by common fetal membranes. The case herein presented is believed to represent the first recorded instance of unilateral dichorial tubal twins. The marked disparity in size of the two embryos, and the readily apparent difference in developmental age, would strongly indicate superfetation.



Fig. 1.—Left Fallopian tube demonstrating the two distinct amniotic sacs and the marked disparity of development age of the embryos.

### Report of Case

D. L., a 37-year-old housewife, was admitted to St. Joseph's Hospital, Milwaukee, on March 20, 1946, complaining of vaginal bleeding and lower abdominal pain. Her last menses had occurred during the first week of January, 1946. She had been well until three days prior to admission, at which time she consulted her physician because of slight vaginal bleeding and ill-defined abdominal pain. The pain eventually localized in the suprapubic region. The day prior to admission, while in her physician's office, she spontaneously passed a small piece of bloody tissue. This was thought to represent placental tissue, and an incomplete spontaneous abortion was suspected. This impression was

Tumor formation may occur in the supernumerary breast tissue and both fibroadenoma<sup>5</sup> and carcinoma<sup>7</sup> have been reported in breast tissue found in the vulva.

Supernumerary breasts may be discovered for the first time during a physical examination, or the patient may become conscious of a swelling which developed at puberty and which may undergo cyclic changes like normal breasts. In this case, clinically, the lump was considered to be either a lipoma or an enlarged lymph node.

### Summary

A case is reported in which a fibroadenoma developed in supernumerary breast tissue in the perineum. This is a rare abnormality.

The author wishes to thank Dr. W. P. Tew, Professor of Obstetrics and Gynecology, for furnishing the clinical notes and for permission to publish this case.

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## BILATERAL HARELIP AND UNILATERAL HARELIP WITH CLEFT PALATE IN FRATERNAL TWINS

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**A**BNORMAL development of the upper lip in twins associated with a deformity of the palate in one is believed to be extremely rare. A review of this subject in the available literature revealed one somewhat similar case. In 1928 Lévy<sup>1</sup> reported this maldevelopment in single-ovum male twins both with unilateral harelip on the right. In one of these twins, the palate was also involved.

### Case Report

The mother was a 30-year-old white gravida iii, para i, estimated date of confinement, July 7, 1946. She was admitted to the hospital in mild labor July 3, 1946. On admission, the cervix was found effaced and 3 cm. dilated. One twin was presenting in right occipitoanterior position with the second twin lying transverse.

The patient was married nine years prior to admission, and had one normal child seven years of age. She gave a history of a spontaneous abortion of a six weeks' gestation in September, 1945. She had the usual childhood diseases without sequellae. Cholecystectomy and appendectomy in 1940, and tonsillectomy in 1941. Family history was noncontributory, except for delivery of twins by her grandmother and by her husband's aunt. Her menstrual history was normal.

Prenatal course was uneventful except for slight vaginal bleeding during the second and third months. Blood pressure was 130/80 consistently after the twelfth week. The presence of twins was suspected at the fifth month when the fundus reached 28 cm. above the symphysis. She gained 28 pounds in weight.

Examination on admission revealed a well-developed and well-nourished 30-year-old white woman, 64 inches in height, weighing 153 pounds. Other than a well-healed cholecystectomy scar and findings associated with twin pregnancy, physical examination was essentially negative.

Labor progressed uneventfully. The first twin, a male, delivered from the right occipitoanterior position by low forceps and perineotomy after five hours and five minutes of labor, weighed 5 pounds, 15 ounces, and revealed a bilateral harelip. The second sac ruptured spontaneously almost immediately with the release of about 300 c.c. of fluid, and the second twin, also a male presented as a footling breech and was delivered five minutes later. This infant weighed 5 pounds, 6 ounces, and was found to have a unilateral harelip on the left with cleft palate. Separate placentas, one about three-quarters as large as the other, were expressed intact. Both cords were attached eccentrically. Except for the abnormalities listed above, no deformities of either child were discovered.

### Comment

A case of fraternal twins, one with bilateral harelip and one with unilateral harelip and cleft palate is reported. The rareness of the condition is attested by a review of the available literature which revealed a report of a similar condition in identical twins, but no similar case of fraternal twins.

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confirmed by a consulting gynecologist, and the patient entered the hospital for dilatation and curettage the following morning.

Physical examination at the time of admission was negative except for slight abdominal tenderness. Vaginal examination revealed a slightly enlarged soft uterus. The cervix was soft and open. No adnexal masses were palpated.

A dilatation and curettage was performed under general anesthesia at 10:15 A.M., March 21, 1946. A large amount of hemorrhagic tissue was removed. Histologic examination subsequently revealed this to be composed of decidual tissue, without chorionic villi.

Following the operation the patient appeared to be in good condition. At 11:15 A.M., however, she suddenly became markedly dyspneic and, despite stimulation, expired one and one-half hours after the surgical procedure.

On postmortem examination, the abdominal cavity was found to be distended with a large amount of liquid and clotted blood, which formed a complete cast of the peritoneal cavity. The uterus was slightly enlarged and soft. The endometrium was partially denuded.

The left Fallopian tube was markedly swollen in its middle third, measuring 4 cm. in diameter. The external surface was of a dark purplish-red color, and smooth except for several small irregular defects. From these protruded small fragments of hemorrhagic placental tissue and a bulging thin translucent membrane. The fimbriated end of the tube was adherent to the left ovary in which a large corpus luteum was noted. Section of the tube after fixation revealed a twin pregnancy (Fig. 1). The embryos lay in distinct amniotic sacs separated by hemorrhagic placental tissue 7 mm. in thickness. The larger sac lay within the ampulla of the tube and measured 4.0 by 2.5 by 2.5 cm. It contained a well-preserved male embryo, 3.3 cm. in length. The smaller sac was located near the fimbriated end of the tube in close proximity to the ovary. It measured 1.8 by 1.8 by 1.7 cm., and contained a well-preserved embryo of undetermined sex, which measured 1.0 cm. in length. The larger embryo displayed well-developed fingers and toes, and was of an estimated three and one-half months' gestation. The smaller embryo exhibited only early limb buds, and was estimated to be seven and one-half weeks of age. Microscopic examination demonstrated that the two amniotic sacs were separated by a thick well-defined layer of chorionic villi.

The remainder of the gross examination revealed slight cerebral edema and chronic fibrous pleuritis. Death was attributed to the very rapid and massive intraperitoneal hemorrhage due to a ruptured tubal pregnancy.

### Summary

1. A case of dichorial unilateral tubal twins is reported. It represents the first recorded instance of dichorial unilateral tubal twins, and the seventy-ninth reported case of unilateral tubal twins.

2. The marked disparity of size and developmental age of the fetuses appears to indicate superfetation.

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*Right ovary*—Portion of ovary was composed of mature luteal cells plus a portion of cortex containing a normal number of primordial follicles. *Diagnosis*: Corpus luteum.

The patient made an uneventful recovery except that she continued to vomit for two more weeks, although the abdomen was soft and the peristalsis was normal. The vomiting was suggestive of the continuation of the suspected twin pregnancy.

The uterus continued to grow. Quickening was noticed on Nov. 17, 1945. On April 9, 1946, the patient delivered spontaneously a female infant weighing 7 lb., 11 oz.

### Comment

This case seems of interest because of the fact that the twin pregnancy went on undisturbed by the operation and by the removal of the corpus luteum.

A twin pregnancy in utero was suggested by the unusual enlargement of the uterus found at operation and the history of the previous twin pregnancy. Gentle handling of the tissues during the operation may improve the chances of successful continuation of a suspected intrauterine twin pregnancy.

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## COMBINED EXTRAUTERINE AND INTRAUTERINE PREGNANCY

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**R**EPORTS of combined extrauterine and intrauterine pregnancies are still rare. Cases with the intrauterine pregnancy carried to term and with a living baby are still more uncommon, according to Lawrence and Elsemore.<sup>1</sup>

### Report of Case

A 41-year-old housewife called me to her home on Aug. 6, 1945, for abdominal pain. This pain, which had begun about seventeen days earlier, was felt mostly in the epigastrium. For about two days the patient vomited and had loose bowel movements after taking a laxative. She also had a slight menstrual flow on August 6, while the first day of the last regular menstrual period was on June 26, or forty-one days ago.

The previous history revealed that the patient had always been in good health. There were five pregnancies, the last one being a twin pregnancy. All six children are living.

Examination revealed a pale woman. The chest appeared normal; the abdomen was somewhat distended. Due to this, the pelvic examination was unsatisfactory. There was some bleeding from the cervix. There seemed to be some doughy swelling in the retrouterine space. The uterus and the adnexa seemed of normal size and shape, with the suggestion of some swelling of the right ovary.

Blood examination revealed a marked anemia, with a hemoglobin of 9.5 Gm. per 100 c.c. of blood; 3,500,000 red cells per c.mm.; a white count of 11,000 cells, with 70 per cent segmented cells, 4 per cent stab cells, and 26 per cent lymphocytes. Blood sedimentation rate (Cutler's method) was found to be 36 mm. in one hour.

We suspected an ectopic pregnancy, and on Aug. 8, 1945, performed a laparotomy through a paramedian incision. There was about one quart of blood in the abdominal cavity. The left adnexa appeared normal, the left ovary did not seem to contain a corpus luteum. The right ovary and the right tube were covered by blood clots and a mass the size of a hen's egg, which appeared to be placental tissue. The right tube was ruptured near the fimbriated end. The uterus appeared unusually soft, about the size of a pregnancy of six weeks, arousing the suspicion of a twin pregnancy in it. The right ovary and right tube were removed.

### *Pathologic Examination.—*

*Gross description:* The right Fallopian tube was ruptured near the fimbriated end and at this point a blood clot protruded. The fimbria retained its flowery appearance. A small hydatid cyst was attached to the mesosalpinx. The right ovary was partially covered with a blood clot and contained a single large corpus luteum of pregnancy.

*Microscopic:* Right tube—Sections showed masses of red cells with typical chorionic villi and typical decidual cells occupying a portion of the lumen and wall of Fallopian tube. Some of the papillae were destroyed, but the majority were compressed. *Diagnosis:* Tubal pregnancy.

iliae and extended about 2 cm. into the femoral artery. The pathologic summary was: "mild atheroma with consecutive incomplete rupture and resulting dissecting aneurysm which is extensive and terminated in hemopericardium with cardiac arrest."

### Discussion

The cause of death in this case is a relatively rare one in itself, there being less than 500 cases reported in all the literature.<sup>9</sup> Men are affected twice as frequently as women, and the highest incidence occurs in the fourth, fifth, and sixth decades of life. Interestingly enough, this patient presented none of the typical clinical evidences of the disease.

No case, to our knowledge, is on record combining a successful postmortem cesarean section with dissecting aneurysm as a cause for death of the mother.

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## POSTMORTEM CESAREAN SECTION

R. O. JOHNSON, M.D., AND T. V. FRANK, M.D., MURRAY, UTAH

*(From the Proceedings of the Clinical Staff Conference, Holy Cross Hospital,  
Salt Lake City, Utah)*

THE dramatic lifesaving procedure of postmortem cesarean section is one that only occasionally occurs, and is rarely terminated successfully. Standard textbooks give the subject little space and no accurate or all-inclusive statistical record can be had. We know that this operation was performed from the earliest times<sup>1</sup> and, while there are no available data on the number of living children obtained, we should have no reason to believe that the percentage of successes among the ancients could have been better than in our present day. Of the 330 reported cases of postmortem cesarean section that occurred during the eighteenth century, only seven living children were recovered. Then, in 1916, Pfaff<sup>2</sup> reported a selected group of 52 well-authenticated cases in which 22 or 42.3 per cent were successful. Since that time, scattered cases have appeared in the literature, notably those of Yule,<sup>3</sup> Joseph,<sup>4</sup> Kuestner,<sup>5</sup> and Roemer.<sup>7</sup> The medicolegal aspects have been reviewed in detail by Campbell and Biller.<sup>8</sup>

### Case Report

Mrs. E. F., aged 34 years, white, gravida iii, was admitted to Holy Cross Hospital at 3:50 A.M., April 28, 1946. Her prenatal course was relatively uneventful. At 2:00 A.M. of the same morning the patient awakened complaining of backache in the lower lumbar region; this was not very severe and was much relieved by standing or walking about. Her attending physician advised, however, that if the pain continued she should go directly to the hospital, since labor might possibly be beginning. The patient presented no complaints at the admission desk, and even had to be encouraged to observe the routine of being conducted to the obstetric division in a wheel chair. Upon entering one of the labor rooms she was being assisted from the wheel chair into bed when she suddenly slumped over in a faint. An extern was present on the scene almost immediately, and he instituted emergency resuscitative measures and the administration of stimulants; when the house physician arrived several minutes later, the patient had expired. No time was lost attempting to locate fetal heart tones; the dead woman was quickly transported to an adjoining delivery room table, a postmortem cesarean section performed, and a living 8½-month baby girl weighing 6 lb., 7 oz. was delivered at 3:58 A.M., just eight minutes after the mother's admission to the hospital. Moderate stimulation and clearing of the air passages had to be employed on the child. At this writing, the child is well and normal in every respect.

A postmortem examination was performed on the mother, and on opening the pericardial sac, about 500 c.c. of dark blood and clot were seen surrounding the heart. There had been some extravasation of blood into the adventitia at the base of the aorta. In the proximal aorta just above the opening of the right coronary there was a V-shaped laceration, one arm of which was 1¼ cm. long and the other 1½ cm. which penetrated clear through the aorta into the adventitia and through the pericardial sac mesial to the right auricular appendage. Dissection had occurred throughout the complete length of the aorta and reached into both common iliaes; on the right, it went out into the external

cent. In the patients in this group who had a blood estrogen determination made, 87 per cent showed a high estrogen level even early in pregnancy. Combining the results reported in this series with a previous series in which vitamin E was used in the treatment of threatened premature labor, there were 92 normal living children born to 109 patients. In the entire series there were only six malformed children, only one of which (with a cleft palate) lived more than three months. If vitamin E is used in the treatment of threatened abortion or premature labor, a product of proved potency must be employed in adequate dosage. Dosage must be determined in each case, depending upon the severity of the symptoms and their duration. Treatment must be continued until term. The authors are of the opinion that routine determinations of blood estrogen should be done on pregnant women when they first report for antenatal care. In this way prophylactic treatment with vitamin E can be given when indicated by a high blood estrogen level. The patient is instructed to report if any slight abnormal symptom develops, such as an area of uterine tenderness, sacral backache, or spotting of blood, when the dosage of vitamin E can be increased.

HARVEY B. MATTHEWS.

### Menstruation, Dysmenorrhea

Cullner, A.: The Relation of Theca Cells to Disturbances of the Menstrual Cycle, *J. Obst. & Gynec. Brit. Emp.* 52: 545, 1945.

In a previous study it was shown that in the baboon, when the theca cells surrounding the ovarian follicles proliferate or luteinize so extensively as to be visible to the naked eye as yellowish plaques or masses, there is often a disturbance of the menstrual cycle. There has been much speculation as to the endocrine function of the theca cells, especially in relation to theca-cell tumors. The author has made a study of the ovaries and uteri obtained at operation on women with excessive bleeding or other uterine evidence of endocrine disorder. Many of these patients were in the 4th and 5th decades of life and had previously had normal cycles and pregnancies. Serial sections of the ovaries were examined.

As the ovaries are removed as a rule only for some gynecologic complaint, it is difficult to establish the incidence of theca lutein cells other than those related to corpora lutea in the normal human ovary. In the author's series luteinized theca cells were found more frequently than was anticipated, but their extent and distribution were not closely related to the severity of the menstrual disorder. The author proposes the following classification of theca-cell proliferations on the basis of their relation to various types of atresia: Group I, corpus thecale luteum, in which the original form of the follicle is retained; in one subgroup (a) granulosa cells are luteinized. Group II, corpus thecale luteum fibrosum, in which granulosa cells are not present, absorption of liquor folliculi has taken place, connective tissue cells fill the cavity and may be surrounded by a hyaline ring; luteinized theca cells are external to this ring. Group III, corpus thecale luteum candicans, in which lutein reactions occur around a collapse corpus atreticum. Group IV, corpus thecale luteum hyalinum, in which there is a lutein reaction around follicles that have collapsed with hyaline tissue invading the cavity. Group V, corpus thecale luteum restiforme, in which a lutein reaction occurs around primordial or small maturing follicles. All these types of theca-cell proliferation with luteinization have been observed in the author's material except Group V, which, however, is theoretically possible. In this material a wide range of endometrial reactions and clinical disturbances was observed, but those could not be correlated with the type of theca-cell luteinization observed in the ovary. In a few cases, normal endometria were found, although luteinized theca cells were present in the ovaries, and there were menstrual disturbances.

From these observations, the author concludes that theca-cell proliferation may occur as part of the process of maturation of the Graafian follicle. Luteinization of theca cells

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Labor, Management, Complications, etc.

de Almeida, A.: Some Considerations Concerning the Medical Induction of Labor, *Matern. e infancia* 1: 25-32, 1945.

The author discusses seventeen methods of medically inducing labor and gives the details of each. His principal indications for the procedure are as follows: hypersensitivity, desire for labor at an appointed time, contracted pelvis and cephalopelvic disproportion, toxemia of pregnancy, cardiac disease, tuberculosis, habitual death of the fetus before term, placenta previa and abruptio placentae, retained dead fetus, fetal gigantism, and fetal erythroblastosis.

J. P. GREENHILL.

Chanal, G.: The Different Methods of Inducing Labor. The Medical Method and Its Results at the Geneva Maternity, *Monatschr. f. Geburtsch. u. Gynäk.* 119: 69-96, 1945.

The Stein medicinal method of inducing labor was used at the Geneva Woman's Hospital in 47 cases. The patients were given 60 Gm. of castor oil in one dose and 1 Gm. quinine sulfate four times at half-hour intervals, alternating with 10 Voegtlen units of Thymophysin, three doses at half-hour intervals. When labor pains were inadequate, Basergin (an ergot preparation) was added to the medication.

In more than 89 per cent of the cases, labor was successfully induced. The incidence of success according to the indication was as follows: premature rupture of the bag of waters, 100 per cent; contracted pelvis, 75 per cent; intrauterine fetal death, 100 per cent; toxemia, 85 per cent; and postmaturity, 86 per cent. The fetal death rate was 6 per cent. Of the three stillbirths, only one could be attributed to the induction of labor. There were no maternal deaths, and the morbidity was 10 per cent.

J. P. GREENHILL.

Biro, S.: Labor in Overweight Women, *Monatschr. f. Geburtsch. u. Gynäk.* 117: 185-200, 1944.

A series of 160 obstetric patients who weighed more than 90 kg. (198 lb.) was studied by the author. It was found that overweight women had a higher incidence of toxemia, more frequent malformations, larger babies, a greater incidence of atony of the uterus, and increased morbidity. In spite of the larger babies, labor was not prolonged. There was an increased frequency of operations and a death rate of 2.5 per cent during labor. These findings indicate that labor in overweight women requires special consideration.

J. P. GREENHILL.

Shute, Wallace, and Shute, Evan: The Prevention of Premature Labor, *J. Obst. & Gynaec. Brit. Emp.* 52: 570, 1945.

In 63 cases of threatened or actual premature labor, 20 of the patients gave a history of previous abortions or other "abnormal terminations" of pregnancy. These patients were treated with vitamin E, and 46 living infants were delivered, a salvage of 73 per

## Newborn

Brown, Estelle W., Lyon, Robert A., and Anderson, Nina A.: Causes of Prematurity—V. Influence of Syphilis on the Incidence of Prematurity, *Am. J. Dis. Child.* 70: 318, 1945.

The authors state that prematurity was somewhat more frequently characteristic of the offspring of syphilitic women than of the infants of nonsyphilitic women. For the white race the respective percentages were 14 and 9 per cent. For the Negro race they were 17 and 12 per cent.

They observe that the incidence of prematurity among syphilitic women were approximately the same for the two races. The association of syphilis and conditions producing uterine bleeding resulted in a pronounced increase in the incidence of premature delivery.

Specific therapy administered to syphilitic patients during pregnancy had pronounced effects. Therapy was associated with a drop in prematurity rates from 16 to 10 per cent. Among Negro mothers the rates fell from 23 per cent to 6 per cent.

JAMES P. MARR.

Brown, Estelle W., Lyon, Robert A., and Anderson, Nina A.: IV. Influence of Maternal Illness on the Incidence of Prematurity: Employment of a New Criterion of Prematurity for the Negro Race, *Am. J. Dis. Child.* 70: 314, 1945.

The authors found the incidence of prematurity among the offspring of white women who were entirely free from serious infection or other abnormalities during pregnancy was 5.5 per cent, in comparison to 13.5 per cent among infants whose mothers had some illness during pregnancy. The lowering of the upper limit of birth weight for prematurity of the Negro infants from 5 pounds, 8 ounces to 5 pounds, 3 ounces, showed respective percentage of 9.2 and 16.6 per cent.

Approximately 80 per cent of the stillborn infants of both races were offsprings of mothers who had some illness during pregnancy.

JAMES P. MARR.

Norval, Mildred A.: Sucking Response of Newly Born Babies at Breast. A Study of Fifty Cases, *Am. J. Dis. Child.* 71: 41, 1946.

From this study it may be concluded that the average early response of newly born babies to the breast is not a greedy one, but is characterized more by dallying and repetitious trials at nursing. This behavior should be met with patience and with calm attempts to allow the baby to learn the gratification he can get from nursing rather than with vigorous unpleasant stimulation.

JAMES P. MARR.

House, Howard P., and Owens, Harold: Atelectasis of the Newborn: Treatment by Bronchoscopic Drainage, *J. Pediat.* 28: 209, 1946.

The etiology of atelectasis of the newborn is not fully understood. Bronchoscopic aspiration of the newborn infant is relatively a benign procedure when properly performed. The author's report a corrected mortality rate, after eliminating other complications, of 11.7 per cent, or two deaths in seventeen cases of proved true atelectasis.

JAMES P. MARR.

Goldbloom, Alton, and Lubinski, Herbert: Anti-Rh Agglutinins in the Maternal Blood Without Symptoms of Hemolytic Anemia in the Newborn Infant, *J. Pediat.* 28: 83, 1946.

A case is presented in which the Rh-positive infant of an Rh-negative mother demonstrated no clinical or laboratory evidence of a hemolytic anemia of the newborn, although



around atretic follicles may be without clinical significance in ovulatory cycles, but in the presence of extensive thecal luteinization with follicular atresia, disturbances of menstrual rhythm and abnormal bleeding may occur. From the character of the uterine reactions found in association with proliferation of theca cells, neither estrogenic nor progesteronic action can be definitely attributed to them. It is possible that they are responsible for a third ovarian hormone that has an androgenic action, or for a modified secretion that disturbs the balance between the hormones acting during the menstrual cycle. The histologic characteristics of some theca-cell tumors of the ovary closely resemble the theca-cell proliferations in atretic follicles.

HARVEY B. MATTHEWS.

Laqueur, W.: The Glycogen Content of the Uterine Endometrium, *Monatschr. f. Geburtsh. u. Gynäk.* 119: 223, 1945.

The author studied the glycogen content of the endometrium in 48 regularly menstruating women. The results were compared with the morphologic findings. No difference was found between the glycogen content of fertile and sterile women. During the proliferative phase the glycogen value averaged 0.27 per cent, whereas in the secretory phase it averaged 0.86 per cent. These fluctuations can be explained by the differences in morphology. The authors failed to find a glycopenia as was described by Zondek and Stein.

J. P. GREENHILL.

Béclere, C., and Simmonet, H.: Hypohormonal Amenorrhea. Its Treatment by a Single Weak Dose of Estrogen-Progesterone, *Presse méd.* 53: 278, 1945.

In 1941 the authors pointed out that there are two distinct kinds of amenorrhea—hypohormonal and hyperhormonal. In the cases of hyperhormonal amenorrhea in young girls, estrogens are contraindicated as are also the gonadotropins. Therapy by means of progesterone alone produces remarkable cures in these cases. In cases of hypohormonal amenorrhea, the usual treatment is by means of large doses of estrogen, but the authors maintain that this treatment is not only fallacious but harmful. They insist that the correct treatment is a small dose of estrogen to which is added some progesterone. The dose recommended is 1-5 mg. estrogen plus 10 mg. progesterone given once. This will produce regular and normal menses.

J. P. GREENHILL.

### Miscellaneous

Hüssy, P.: Studies of Infanticide, *Monatschr. f. Geburtsh. u. Gynäk.* 120: 57, 169, 1945.

There has been an increase in infanticide in Switzerland partly because of the new law which limits the medical indications for interruption of pregnancy, partly because of the lenient sentences meted out for this horrible crime, and finally because jurors are readily disposed to acquit the murderers. The same is true of other countries, particularly France. In most cases, the defense lawyers claim the murder was committed while the patient was in an abnormal state of mind. However, true transient insanity in cases of infanticide is rare. In cases of precipitate labor, the accused should be exonerated.

In many cases the murder is deliberate, as proved by the fact that the birth is secret. If the secret labor does not conceal everything, the only alternative is infanticide. The most common form of death is suffocation. In all cases of infanticide it is important to obtain a complete history, make a thorough examination of the patient and baby, including a postmortem examination and careful inspection of the site of the crime. One must decide whether the child was born alive and viable and whether the accused secretly gave birth.

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or in any bleeding of undetermined origin. Obviously, the condition incurs no danger to the mother, since the blood loss is entirely from the fetus. The fetal mortality is high.

Three cases are reported. In the first case which was delivered, the baby was delivered through an opening in the membranes which lay directly between two umbilical vessels. The second case is one who began bleeding immediately after artificial rupture of the membranes. Intermittent bleeding continued throughout labor. A living, male infant was delivered. A velamentous insertion of the cord was found after delivery of the placenta in which one vessel ran completely around the amniotic sac at its greatest circumference to join the placenta on the opposite side. This vessel was ruptured and was, undoubtedly, the site of origin for the bleeding which followed rupture of the membranes. The third case is one in which the baby delivered through an opening in the amniotic sac located between two vessels. There was no fetal mortality in these three cases.

WILLIAM BICKERS.

### Pregnancy: Physiology, Diagnosis, etc.

Do Amaral, C.: Experience With Frank and Berman's Modification of the Aschheim-Zondek Test, *An. brasil. de ginec.* 20: 108, 1945.

After giving a description of Aschheim-Zondek's original test and later modifications of it by different investigators, the author discusses Frank and Berman's technique by which, using female rats, the readings can be made within eight hours. This test was used by the writer in 227 cases. Confirmation of results was possible only in 66 instances; 34 were positive, 29 negative, and 3 errors. The author favors this test due to the ease on handling rats, low cost, shorter time for the readings, and accuracy.

J. P. GREENHILL.

Leverton, Ruth M., and McMillan, Thelma J.: Meat in the Diet of Pregnant Women, *J. A. M. A.* 130: 134, 1946.

The women secured for this study were all private patients of adequate economic status. All of them had histories of good health and were under 33 years of age. To insure that the women were receiving plenty of meat, they were supplied with a 5-ounce serving of lean meat daily which they ate in addition to their self-chosen diets and at times other than the main meal. The women who received the additional meat had consistently better hemoglobin and red-cell values at all times than did their experimental partners who received either B complex or no supplement. The protein content of the self-chosen diets averaged 58 Gm. daily for each group of subjects. The additional meat contained 25 Gm. daily, bringing the total to 83 Gm. daily. The values at the end of three months after delivery were similar to those one month after delivery. All of the pregnancies and deliveries were without complications. The group eating the additional meat had better results with lactation.

WM. BERMAN.

### Pregnancy: Complications, etc.

Dutra, L. H.: Chorea Gravidarum. Treatment With Vitamin B6 (Two Cured Cases), *Rev. de ginec. e d'obst.* 38: 1944.

Two serious cases of chorea gravidarum were completely cured by the author by the administration of vitamin B6 without any other therapy. One patient received 600 mg. and the other 800 mg. of chlorinhydrate of pyridoxine applied intramuscularly in ampules containing 50 mg. These cases support the results obtained by Schwartzman in the treatment of Sydenham's chorea and Rabin and Duek's results in chorea gravidarum. Hence, in these diseases there is deficiency of vitamins, especially B6.

J. P. GREENHILL.

anti-Rh agglutinins were shown to be present in the maternal blood at the time of delivery. This demonstrates that a consideration of certain variable factors in the pathogenesis of the disease in addition to differences in Rh type.

JAMES P. MARR.

Holt, J. P., Schockaert, J. A., Renaer, M., and Vandenbroncke, J.: *The Blood Volume and Physiologic Icterus of the Newborn*, *Monatsehr. f. Geburtsh. u. Gynäk.* 120: 141-146, 146.

In the opinion of the authors, physiologic icterus in the newborn occurs when hyperbilirubinemia, which exists in all newborn babies, exceeds a certain amount. Hyperbilirubinemia in the newborn is caused partly by secretory insufficiency of the liver. The hyperbilirubinemia leads to icterus when it reaches a high amount through increased hypofunction of the liver or when functional insufficiency is combined with more or less increased hemolysis.

J. P. GREENHILL.

Fender, Frederick A., Neff, William B., and Binger, Grace: *Convulsions Produced by Fetal Anoxia; Experimental Study*, *Anesthesiology* 7: 10, 1946.

The authors were interested in the possible relationship between anoxia and the convulsive states in the human and set up a series of experiments on dogs in an effort to show that anoxia in the unborn fetus or newly born young can lead to convulsive states later on in life. The central nervous system demands a great amount of oxygen for normal function. This fact has been known for many years, but not until recently has any recognition been accorded the role of anoxia in the unborn fetus or the newly born child to future development of convulsive seizures. In summarizing their work, the authors state that nerve tissue is more sensitive to oxygen deprivation than any other type of body tissue. This tends to be most marked at the highest neurologic levels. It is further believed that fetal and neonatal anoxia in humans may play a major part in the development of epilepsy.

HARVEY B. MATTHEWS.

## Placenta

Kuntz, A. C., and Mussi, F.: *The Treatment of Placenta Previa*, *Bol. Soc. de obst. y ginec.* 23: 793-798, 1944.

The authors report that the ideal treatment for placenta previa is spontaneous labor after rupture of the membranes, if the fetus is living and viable. If the fetus is dead, the authors recommend rupture of the bag of waters and delivery by the use of the presentation which is the least damaging to the mother, even if a craniotomy must be performed.

J. P. GREENHILL.

Rucker, M. Pierce, and Tureman, Garnet R.: *Vasa Previa*, *Virginia M. Monthly* 72: 202, 1945.

Vasa previa is defined as an anatomical abnormality of the fetal membranes in which a placental vein traverses the amnion in such a manner as to cross at the internal os. The incidence of velamentous insertion of the cord is approximately one per cent. It is more common in twin than single pregnancies; it carries a definite risk to the fetus. The umbilical vessels may be compressed, causing asphyxia, or one of the vessels may rupture. Antepartum diagnosis depends upon palpating the pulsating vessels through a partially dilated cervix. Rupture of the veins most often occurs at the time of the rupture of the membranes; however, rupture of the vessels with membranes intact has been reported. The condition should always be considered when profuse bleeding follows rupture of the membranes,

of puerperal infection was 41 per cent. There was no proof that pregnancy aggravated the cancer. Treatment depended on the grade of the cancer and the duration of the gestation. The incidence of five-year cures was 17 per cent.

J. P. GREENHILL.

Barnes, Josephine, and Browne, F. J.: Blood Pressure of Relatives of Patients With Toxemia of Late Pregnancy, *J. Obst. & Gynaec. Brit Emp.* 52: 559, 1945.

It is well known that a tendency to high blood pressure and the diseases associated with it may affect members of the same family and this tendency is generally supposed to be hereditary, although this conclusion is based on studies of individual families rather than on a statistical survey. Many cases have been reported of eclampsia occurring in members of the same family; and a tendency to hypertension has been noted in families of patients who have developed eclampsia or late toxemia of pregnancy.

Blood pressure was recorded in 226 relatives of 129 patients admitted to the hospital with late toxemia of pregnancy, and in 66 relatives of 47 patients admitted toward the end of pregnancy without toxemia. There was no essential difference in the levels of the blood pressure in the relatives of the toxemic and nontoxemic pregnant patients except in the group of toxemias classified as essential hypertension of pregnancy. In this group the incidence of hypertension in the family was higher than in other types of toxemia or in nontoxemic patients. Of 18 mothers of the patients with essential hypertension of pregnancy, whose blood pressure was recorded, 16 showed marked hypertension. On the basis of these findings the authors conclude that it is rarely necessary to interrupt pregnancy in patients with essential hypertension unless the hypertension is of the malignant type. Patients with malignant hypertension should be advised not to become pregnant. Patients with a familial history of hypertension should be discouraged from having children, except in those cases in which the manifestation of hypertension have occurred often and at an early age.

HARVEY B. MATTHEWS.

### Puerperium

Palik, F., and Rechnitz, K.: A Case of Late Hemorrhage in the Puerperium, *Monatschr. f. Geburtsh. u. Gynäk.* 117: 74-80, 1944.

In nine cases of delayed hemorrhage, four after full-term labor and five after abortions, the cause of the bleeding was found to be hyaline degeneration of the decidua. The degeneration probably began before the onset of labor due to activity of the trophoblast. The liquefaction and expulsion of the decidua were probably interfered with because the fibrinous degenerated decidua failed to set up a round cell demarcation. Treatment in such cases should consist of instrumental removal of the remnants of decidua. In cases of abortion, the early onset of menstruation may produce spontaneous healing.

J. P. GREENHILL.

Roblee, Melvin A., and Moore, Sherwood: "Lipiodol" Pulmonary Emboli Following Hysterosalpingography, *South. M. J.* 38: 89, 1945.

A complete angiogram of the uterus and broad ligaments was obtained by the accidental injection of lipiodol into the uterine veins. This resulted from a defect in a cesarean scar which was separated at the time of the injection. The oil was visualized in the pulmonary vessels.

About 9 c.c. of lipiodol was injected before any leaking about the cannula was noted. At this time, the patient complained of pain and of breathing more rapidly. She had fullness in the chest, but there was no pallor, sweating, or dizziness. X-ray exposure immediately after the injection showed the complete angiogram. Fifteen minutes after the injection, it showed the oil in the iliac veins and the entire pattern of the bronchovascular tree. An irregular cough with hematemesis persisted for several days, and then the patient had a complete recovery.

WILLIAM BICKERS.

Wilson, Andrew, and Barr, J. James: *Myasthenia Gravis and Pregnancy*, *J. Obst. & Gynaec. Brit. Emp.* 52: 584, 1945.

In the case reported, the patient had had myasthenia gravis for eighteen months; symptoms were satisfactorily controlled by prostigmin (15 mg. three times a day) and ephedrine ( $\frac{1}{2}$  gr. twice a day). When she became pregnant, there was no change in her condition until the beginning of the second trimester, when a slight increase in the amount of prostigmin was necessary (60 mg. daily). Labor was normal and delivery spontaneous; there was no evidence of any exhaustion of the voluntary musculature, and no signs of any inertia or fatigue of the uterus. There was a transient mild relapse of the myasthenia gravis, necessitating another slight increase in the dosage of prostigmin during the first five days after labor. By the fifth day, the patient's condition was the same as in the last half of pregnancy; and on the ninth day a definite remission of the myasthenia gravis began which continued for nine months, so that symptoms were controlled by a smaller dose of prostigmin than was required before pregnancy; the patient nursed the child for seven months of this period. After this nine months' remission, the dosage was raised to the prepregnancy level for adequate maintenance. The child was normal at birth and has developed normally. This case and a review of the literature lead the author to conclude that there is no indication that pregnancy, labor, or nursing affects the course of myasthenia gravis adversely, if the patient is adequately treated with prostigmin and ephedrine.

HARVEY B. MATTHEWS.

Thomas, Rufus C.: *Rupture of the Rectus Abdominis Muscle During Pregnancy*, *J. Obst. & Gynaec. Brit. Emp.* 53: 580, 1945.

The author has previously reported a case of rupture of the rectus abdominis muscle during pregnancy, and reports a second case in this article. In this case the patient had had five previous normal pregnancies and deliveries and one abortion. She was admitted to the hospital when about 33 weeks pregnant, with a history of bronchitis and pain in the abdomen when she coughed; a "lump" had also been noticed in the region of the right rectus muscle. While a diagnosis of concealed accidental hemorrhage was made, the uterus was softer than it would be with such a hemorrhage that produced abdominal tenderness. While under observation she developed typical symptoms of internal hemorrhage, and operation was done. This showed a tear in the right rectus muscle with bleeding from a branch of the deep epigastric artery and another smaller vessel; blood clots were removed, the bleeding arteries ligatured, and a pack placed along the deep surface of the rectus muscle, and brought out through the lower end of the incision, which was then closed. On the fifth day after operation, the patient was delivered of a stillborn child. The patient finally made a good recovery, which was delayed by a reaction to an incompatible blood transfusion. A review of the literature shows this to be the thirty-second case reported of rupture of the rectus muscle during pregnancy; the correct diagnosis was made before operation in only nine of the 32 cases. Cullen's sign was present in five of the cases, including the case reported. The maternal mortality was 13 per cent, the fetal mortality about 50 per cent. Conservative treatment is justified in these cases only if the patient's condition remains good; if signs of increasing hemorrhage and shock develop, operation is indicated.

HARVEY B. MATTHEWS.

Riesco, A., and Rodriguez, F.: *Cancer of the Cervix and Pregnancy*, *Bol. Soc. Chilena de obst. y ginec.* 10: 93-118, 1945.

At the National Institute of Radium in Santiago, Chile, 33 cases of cancer of the cervix complicating pregnancy were observed. This represented an incidence of 0.31 per 1,000 pregnancies. The most frequent age of the patients was between 28 and 30 years. The patients were seen on an average of four months after the onset of symptoms. In 21 per cent the patients had Group I cancer. In 93 per cent of the cases, the carcinoma was of the squamous-cell type. Labor was premature in 27.3 per cent, and a similar number had abortions. Among the 19 cases of abortion or delivery through the vagina, the incidence

## Correspondence

### Maternal Weight Gain and the Newborn Infant

To the Editor:

In 1945, Beilly and Kurland presented a careful study of the relationship between maternal weight gain and the weight of the newborn infant which demonstrated a positive correlation involving very small increases in the newborn weight in proportion to maternal gains (AM. J. OBST. & GYN. 50: 201, 1945). Klein has now presented (AM. J. OBST. & GYN. 52: 574, 1946) a smaller group of cases on the basis of which he concludes that no such correlation exists. Unfortunately, despite his statement to the contrary, Klein has failed to submit his data to statistical analysis.

In Tables I and VII of his paper, Klein compares maternal gain with newborn weight by establishing arbitrary weight groups. In each table the tendency of the larger gainers to have heavier babies is obvious. He assails this by comparing groups which include minor fractions of his total number of cases, making, for example, no effort to correct for unequal assortment of male and female newborns, in spite of the demonstration in Table V that males weigh more. The same trend is apparent in Table IV, in which the mothers are grouped by parity. Here Klein expresses the essence of his entire discussion in the statement that "where differences are found, they are usually not very great."

Table III is of value because it deals with large groups in which chance irregularities of distribution of sex, parity, age, and other possible factors may be expected to cancel out. This expectation can be verified in part by reference to the other tables in Klein's report. Table III tests a simple proposition: Mothers who gain 20 pounds or more are more likely to have babies who weigh over 7 pounds than are mothers who gained less than 20 pounds.

The data, slightly rearranged, are:

NEWBORN WEIGHT	MATERNAL WEIGHT GAIN	
	20 POUNDS OR MORE	LESS THAN 20 POUNDS
Less than 7 pounds	83	100
7 pounds or more	244	140

Mere inspection is sufficient to show that the proposition is supported by the data. The majority of the mothers of babies weighing less than 7 pounds had themselves gained less than twenty pounds (100:83), whereas the majority of mothers whose newborns weighed 7 pounds or more had gained 20 pounds or more (244:140). The possibility that this difference is due to chance is less than 5 in 10,000.<sup>1</sup> Klein attacks the conclusion which his data indicate only by pointing out an absence of gross relationships between averages of weights in the four subgroups, phenomena which this table is not adapted to test. He also criticizes Beilly and Kurland for concluding that every one pound gain in the mother's weight is accompanied by an 0.25 pound increase in the newborn's weight. Of course, such a conclusion is contrary to common sense and everyday clinical observation, and review of their paper reveals that this assertion, made on p. 203, must be a typographical error.\* On the basis of their graph and data on p. 204, the increase in baby's weight for each pound of gain of the mother is 0.025 pounds. Their equation agrees surprisingly well with the data in Klein's Table I.

\*Personal communication with Dr. Jacob Beilly confirms the fact that a typographical error was made and that the correct figure is 0.025 pounds.

## Anesthesia

Hartzell, Homer C., and Mininger, Edward P.: *Bronchopneumonia Following Ether Anesthesia in Obstetrics, Surg., Gynec. & Obst.* 82: 427, 1946.

The authors report a series of 20 cases of bronchopneumonia observed at the Cleveland City Hospital, which followed delivery under ether inhalation anesthesia. A search of the literature failed to reveal a similarly large series, although the authors found two reports of serious aspiration pneumonia following obstetric anesthesia. It was felt that pre-anesthetic medication, favoring suppression of the cough reflex, prolonged gastric evacuation during labor, and the fluidity of the gastric contents, all played a part in contributing to this condition. It is of interest to note that 15 of the 20 cases received ether by cone rather than by the more modern techniques. There were no fatal cases in this series and, although half of the cases had chemotherapy, the authors did not feel that this played any important role.

L. M. HELLMANN.

## Malignancies

Erskine, Arthur W.: *Indications and Limitations of Transvaginal Roentgen Therapy for Cancer of the Cervix, Radiology* 5: 458, 1946.

The author feels that the transvaginal roentgenization of the cervix is the most valuable contribution to radiotherapy since the adoption of the international unit, and is by far the most efficient method of destroying the primary tumor. Vaginal atresia is a definite contraindication to the use of this method. In cases of vaginismus, the treatments are sometimes given under nitrous oxide or intravenous anesthesia. Pelvic infection and pyometra postpones transvaginal therapy until the infection is cleared. In hopeless cases, when it appears futile to expect a cure, it is good judgment to restrict treatment to cases in which response to the cross fired treatment indicates a radiosensitive tumor. This treatment may also be used to control hemorrhage.

WILLIAM BERMAN.

Pasi, P. L., and Di Guglielma, L.: *Transformation of a Cervical Polyp into Carcinoma, Obst. y ginec. latino-am.* 3: 720-723, 1945.

The author reports a case that was clinically diagnosed as cervical polyp which, on histologic examination, was found to be a squamous carcinoma. This is a proof that the clinical examination alone is not sufficient to decide about the benignity or malignancy of cervical polyps, and that the belief they always are innocuous is wrong. The best way to avoid unpleasant discoveries is the histologic examination of all extirpated pieces.

J. P. GREENHILL.

Pelitier de Queiroz, A.: *Total Cancer of the Uterus, Obst. y ginec. latino-am.* 3: 713-719, 1945.

The author reports a case of massive invasion of the whole uterus—corpus, isthmus, and cervix—by a carcinoma of the intermediate variety, in a patient aged 66 years. Considering the total invasion of the uterus on the surface and in the depth—in the endometrium only a thin muscular sheet was left, in contrast with the integrity of the parametrium, paracolpos, and vagina—the author includes this case in the group of total carcinomas.

This sort of cancer is an anatomic or surgical finding, but not a clinical entity.

He distinguishes total cancer from the multiple type of cancer. J. P. GREENHILL.

male newborns in the series which may be considered as a fairly equal distribution. Beilly and Kurland also based their conclusions upon the total number of babies. They stated that the correlation which they had postulated did not follow when male and female newborns were compared separately (p. 203).

In Table III, the data of which Dr. Kaiser had rearranged, I believe there is further evidence against the existence of a *direct* correlation between the maternal weight gain and the average weight of the newborn. Although 57.67 per cent of the mothers had gained 20 or more pounds during pregnancy, 67.72 per cent of the babies had weighed 7 or more pounds at birth. I agree with Dr. Kaiser that from the table it is obvious that more women who had gained 20 or more pounds (74.61 per cent) had had babies whose birth weight was 7 or more pounds. However, 58.33 per cent of the 240 women who had gained less than 20 pounds also gave birth to infants whose birth weight was 7 pounds or more.

It is still my opinion that although the data I have presented indicate a tendency for the average weight of the newborn to increase as the average maternal weight gain rises, they do not demonstrate a proportionate relationship between the two. In my conclusions I apparently failed to make this point clear.

JOSEPH KLEIN, M.D.

HARTFORD, CONNECTICUT  
DECEMBER 14, 1946.



Without the raw data, it is difficult to go further with Klein's material. However, as has been shown, on the basis of what he has presented there is no doubt that a relationship between maternal weight gain and newborn weight does exist.

The basic difficulty with Klein's report appears to be a failure to employ appropriate procedures in the handling of data. This is particularly disappointing because of the author's assiduity which is manifest in the size of the series and in the detailed information offered in the tables. Actually, what he presents in the discussion of his material is numerical description and comparison and not statistical analysis. Biologic variation is sufficiently familiar so that individual exceptions or irregularities in groups too small to be a representative sample should never be employed to disprove general propositions, especially in such matters as weights and weight gains. Furthermore, demonstration that observed differences are small may or may not prove that no significant differences exist.

Of course a distinction must be made between relationships of statistical validity and those of clinical significance. Whereas a difference of one-fourth pound may be quite reliable in a tabulation of a thousand cases, it may be immeasurable and insignificant at the bedside of a woman in labor. If Klein meant to state that the differences he observed were not of clinical usefulness then that conclusion should have been more clearly stated.

1. This statement is based upon application of the Chi-square test, a procedure widely used in biometrics. The test is based on a comparison between observed and theoretical results. For example, in the entire group of 567 cases, 32.2 per cent of the babies weighed less than 7 pounds. Theoretically, if maternal weight gain has no effect on newborn weight, among 240 mothers who gained less than 20 pounds there should have been 78 babies under 7 pounds ( $240 \times 32.2$  per cent), whereas actually there were 100. Simple arithmetic computation of these differences between observed and theoretical results as they appear in each category of the table yields a value known as  $\chi^2$  which can be reduced to probability by a conversion table.

$\chi^2$  in this example equals 16, which is equal to a likelihood of less than 0.0005. Hence, due to the operation of chance alone, the observed group of results would occur less often than once in 2,000 times. This clearly demonstrates that some biologic factor is operating.

IRWIN H. KAISER, M.D.

DEPARTMENT OF EMBRYOLOGY,  
CARNEGIE INSTITUTION OF WASHINGTON,  
BALTIMORE, MD., Nov. 22, 1946.

### Reply by Dr. Klein

*To The Editor:*

Dr. Kaiser has pointed out that Tables I and VII of my paper demonstrate an obvious tendency for women who have gained more weight during pregnancy to have larger babies. My concurrence in this observation was stated in the original article—"Although the table indicates a tendency for the average weight of the newborn to increase as the mother gains more weight during gestation, it conclusively demonstrates that there is no proportionate relationship between the two" (p. 575). The principal point upon which I took issue with Beilly and Kurland was that there is a progression in the increase of the average weights of newborns which parallels the maternal weight gain during pregnancy. The results tabulated in Table I of each series are similar only up to the 25 to 30 pounds weight-gain groups. Whereas the other writers found continued increases in the average weight of newborns as the maternal weight gain increased, I observed that in the next group of mothers, the average birth weight of the newborn was the same as that of the preceding group, despite an increase of 4.26 pounds in the average maternal weight gain. In the next two groups, there was a decrease in average newborns' weight in the presence of pronounced increases of average maternal weight gain.

Dr. Kaiser stated that in arriving at conclusions based on Table I, I had failed to correct for unequal assortment of male and female newborns. There were 282 male and 285 fe-

## International Congress of Obstetrics and Gynecology Dublin, Ireland, July 7 to 12, 1947

The program for the Congress includes seven sessions to be devoted on successive days to the following topics: history of midwifery, puerperal sepsis, eclampsia, sterility, fetal and neonatal mortality, and shock in obstetrics. Representative speakers from several countries will discuss these topics, including the British Isles, New Zealand, the United States, Australia, South Africa, Sweden, Palestine, Denmark, Canada, and elsewhere.

Information about travel routes, hotel accommodations, etc., may be obtained from the local offices of Messrs. Thos. Cook and Sons.

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## American Congress of Obstetrics and Gynecology

The program of the Third American Congress on Obstetrics and Gynecology to be held September 8 to 12, 1947, in St. Louis will feature general sessions for all groups making up the Congress, as well as smaller individual group meetings and round table discussions. The morning sessions will be panel-type presentations of the following subjects: Tuesday, Sept. 9: Anesthesia and Analgesia; Wednesday, Sept. 10: Cancer; and Thursday, Sept. 11: Cesarean Section.

The afternoon meetings of the medical section of the Congress will consider on Tuesday: Psychosomatic Aspects of Pregnancy; on Wednesday: Pregnancy Complicating Cardiac Disease, Diabetes and Tuberculosis; and on Thursday: Recent Advances in Endocrinology.

Round table discussions from 4 P.M. to 5 P.M. daily will consider such topics as etiology of abortion, asphyxia, fibroids, prolonged labor, infertility, early ambulation, adolescence, treatment of abortion, genital relaxation, ovulation, the menopause, the cystic ovary, uterine bleeding, nutrition in pregnancy, geriatric gynecology, endometriosis, and erythroblastosis.

Concurrent sessions and round tables for nurses, hospital administrators, and public health workers are being arranged.

The popular foreeps and breech demonstrations that attracted so much attention at the Second Congress in 1942 will be increased in number so that eighteen demonstrations per day will be held, six each at 9:00, 1:00, and 5:00 o'clock daily.

A large Scientific and Educational Exhibit is being set up under the direction of Dr. J. P. Pratt of Detroit and a comprehensive Motion Picture Program is being arranged by Dr. John Parks of Washington, D. C. The committees assisting these doctors will review applications by prospective participants late this spring. Anyone wishing to make application for space in the Scientific Exhibit or for time on the Motion Picture Program may obtain the proper blanks from the office of the Congress at 24 West Ohio Street, Chicago 10, Illinois.

## Items

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### The Albert Mathieu Chorionepithelioma Registry of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons

At the last meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held in Hot Springs, Virginia, September 7, 1946, Dr. Albert W. Holman of Portland, Oregon, made a generous monetary gift to the Association for a Registry of material dealing with hydatidiform mole and chorionepithelioma. This gift was to be considered as a memorial to the late Dr. Albert Mathieu, who had been deeply interested in this subject and who, with Dr. Holman as a joint author, had published a number of valuable papers dealing with it. The gift was accepted by the Association, and a committee was appointed to carry out the purpose of the Registry. This committee consists of the following Fellows of the Association: Dr. Emil Novak, chairman; Drs. Albert W. Holman, Willard R. Cooke, Robert A. Ross, James R. Miller, and Herbert E. Schmitz.

The importance of this Registry lies not so much in the numerical frequency of the lesions to be studied, as in the fact that they represent a field in which misinterpretations have probably been proportionately more frequent than in any other in the domain of obstetric pathology. As a matter of fact, there is no crystallization of opinion as to histologic criteria of malignancy in lesions of this group, and no one laboratory can expect to accumulate a sufficient number of these relatively rare lesions to permit of conclusive studies on this point. It is hoped that clinics and laboratories throughout the country will cooperate by sending in material of this sort, so that the Registry will be able to accumulate a large storehouse of material which can be authoritatively studied from a pathologic standpoint, and for which there will be adequate clinical data, as well as follow-up studies.

For the present at least, the material of the Registry will be stored in the laboratory of Gynecological Pathology of the Johns Hopkins Hospital, Baltimore, Maryland, and communications and material may be directed to the chairman of the committee, Dr. Emil Novak, 26 E. Preston Street, Baltimore, Maryland, or directly to the Laboratory. Simple clinical forms to facilitate the supplying of adequate clinical data will be mailed to those sending in material.

Sections or gross material from all cases of hydatidiform mole, whether thought to be benign or malignant, as well as those in which chorionepithelioma has been diagnosed or suspected, are earnestly solicited. They will receive careful study by all members of the Registry Committee, and at its conclusion a report will be sent to the donors of the material as to its classification, although this will naturally involve a rather long delay. The Registry will make no pretense of conducting a diagnostic laboratory for quick reports on questionable material.

It will be seen that the general purpose of the Chorionepithelioma Registry, as well as its plan of operation, is quite similar to that involved in the Ovarian Tumor Registry, sponsored by the American Gynecological Society. The latter Registry has already accumulated a large number of thoroughly studied ovarian tumors which before many years should yield valuable knowledge of various tumor groups. It is hoped that, in the more limited field assigned to it, the Chorionepithelioma Registry may be equally successful in collecting, studying, and classifying material which may yield valuable new knowledge in the future.

of Jamestown. One must not, however, underestimate early American medicine, especially that of the period which began about 1750 and which characterized the remainder of the eighteenth century. Progress, during that time, was temporarily inhibited by the American Revolution but, following the war, it was definitely stimulated. Many courageous American physicians lived and worked during those pioneer years. They were men of outstanding personality, with good classical educations and with a knowledge of contemporary medical science gained in London, Edinburgh, Paris, Montpellier, and Leyden, the accepted centers of medical science and education of their day. Of these places Edinburgh seems to have been the most popular. The school was founded by Scotch pupils of Boerhaave (1668-1738) and it is said that the books and the principles of medical practice of that great Dutch clinical teacher and educational leader remained "dominant" in American medical practice until near the end of the eighteenth century. For many years, before and after the American Revolution, our predecessors, with the kindly help of some of the best clinicians in medical history, received their training in these centers during very important years in our medical progress. At home, these men passed on what they had learned to their associates by means of papers and courses of lectures and, through the old apprenticeship system functioning at its best, they helped to supply younger men with their knowledge of the basic sciences and with the much needed clinical training of the sick room. Most important of all they awakened in them an abiding desire for higher medical learning. It is well known that numerous prominent Americans, among them Benjamin Franklin, realizing the need of better medical education in the colonies and having an active desire to aid in its progress, were able, through their acquaintance and their influence abroad, to establish helpful medical contacts for our students and to aid greatly in their education.

It was in this way that we advanced at that period and that our medical schools were made possible. This craving for foreign study became so deeply ingrained in the traditions of our profession that only after World War I, with the decline of the European schools and the rapid improvement of our own, were our ambitious young men willing to complete their medical education at home. The average early American physician of this period, however, was unable to obtain the advantages of foreign study. His very limited preliminary schooling with his meager medical education was a poor preparation for practice. As a rule, however, he was an honest and practical counsellor, was a leader in his community, and was usually greatly loved as an individual.

The progress of American medicine in the early and middle decades of the nineteenth century and to the end of the Civil War in the United States was not outstanding. By this time our university medical schools and hospitals had been established and many independent schools had sprung up over the country, largely displacing the old apprenticeship system so important in the eighteenth century. The number of thoroughly educated physicians had greatly increased. Some of them, McDowell, Sims, Holmes, and many others had made conspicuous individual contributions to medical science. Advanced medical training, however, was still limited to a small proportion of our pro-

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*Fifty-Seventh Annual Meeting  
Hot Springs, Va., Sept. 5 to 7, 1946*

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## **PRESIDENTIAL ADDRESS\***

### **The Advance of American Medicine**

LEWIS F. SMEAD, M.D., TOLEDO, OHIO

FIRST of all, I desire to thank you for the very great honor of acting as your presiding officer for a term which, by the fortunes of war, has been extended over a period of two years. No honors, I am sure, are more deeply appreciated than those bestowed by one's friends and professional associates. In these years, fraught with such perils to our countries and to our profession, I have faced the duties of this office in sincere humility, especially as I have recalled the fine men who have preceded me and the other wonderful Fellows of this association who have come and gone over the years.

World War II is passing into history. It is, therefore, fitting at this time that we express our gratitude and do honor to the members of our profession, especially to those of this organization who have served in the armed forces of Canada and of the United States. They have given of their time and of their lives to carry help to our sick and wounded. They have secured results such as have never before been obtained in time of war. We are very proud of these men and of the profession which has made the results of their work possible, not only by epoch-making discoveries in medical science, but also by the teaching, year after year, of the sound basic principles of medicine and surgery.

The growth of medical education and of medical practice in North America progressed very slowly in our scattered cities and communities during our pioneer days. Our first medical schools, hospitals, and medical libraries were not established until more than one hundred and fifty years after the founding

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\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

the nineteenth century, and remained there until nearly 1914. Doctor William S. Halsted, who was greatly influenced by German surgery and was a student in that country at an early date, made some significant observations in his paper delivered as "The Annual Address in Medicine" at Yale University in 1904. He relates: "In the year 1876, the year when I first walked the wards of Bellevue Hospital, New York, the dawn of modern surgery in America had hardly begun." Again he states: "Thirty years ago as I sat upon the benches, often seven hours a day, listening to medical lectures, I was so impressed with the characters and lives of some of my teachers that I believed they represented all that was most advanced in medicine. But a day in Halle, at the clinic of Volkmann, was a revelation to me. There I heard by one of the young assistants at the early morning clinic an impromptu discourse on epithelioma at which I marvelled. At home the whole subject of tumors had been treated of in one lecture, in one hour, in the "tumor lecture." Again, he asks the question: "Why was Germany the country first to adopt antiseptic surgery? Why did almost every surgeon in every German University eagerly embrace Lister's system almost at the same moment and as soon as it was clearly presented? The answers to these questions are, I believe, to be sought mainly in the character of the scientific and practical training of surgeons in Germany."

Fortunately, by the last decade of the nineteenth century, well-organized and adequately endowed medical schools of a more modern type had been formed in some "five or six" of our universities. Anatomy, physiology, physiological chemistry, pharmacology, and pathology, with the rapidly growing subdivision of bacteriology, were no longer included in the general university curriculum, but had become integral departments of the medical school organizations under well-trained, full-time professors who were doing excellent research work. The clinical departments, likewise, were under the leadership of men of unusual training and ability. Most important of all, small groups of our best young men, attracted by these opportunities, were beginning a fine type of prolonged, personally supervised graduate training in an atmosphere conducive to higher medical learning. These young men and their pupils were later the professors and the teachers in the better type of medical school which made possible the rapid advancement in medical education of the last twenty-five years.

Unfortunately, such ideal conditions were not universally present. There were, as yet, not enough outstanding medical leaders and teachers in America with a true conception of the real meaning of advanced medical education, and there were entirely too few adequate endowments for medical schools of a modern type. The appearance, in 1910, of the Flexner report and the publication, in the same year, by our Council on Medical Education, of its first classification of medical schools and of its standards for an acceptable school, were followed by a revival of medical education in America which is still in progress. This upheaval in our educational system also brought to an end the era of the proprietary medical schools. They had long been fighting a losing battle against the rising cost of modern medical education and against the indifference of the public to the crying need of higher professional training in our

fession, and coordinated effort for scientific work was difficult in our scattered communities. Medical education in these years, while advancing slowly was, nevertheless, making very definite progress. The educated people of the time, however, and even our universities, seemed very slow to realize that good medical service throughout America was impossible without higher medical education at home. They did not yet fully comprehend that advancement in medical science is made, not through "theological dogma, metaphysical speculation," nor the pet theories of some forceful personality, but only through a vast amount of careful research in the physical, chemical, and biological sciences and in clinical medicine.

In 1870, Charles Eliot, a great educator and, at that time, the newly elected president of Harvard, found medical education in the United States still in a very primitive state of development. With few exceptions, there were extremely low entrance requirements and poor or almost nonexistent laboratories. Instruction was imparted by lectures from morning until night, and adequate clinical training was available for only a very few. There were many excellent teachers but their interest was blunted by the constant repetition of courses of lectures, often three times each year, to students poorly prepared to profit by their instruction. The final examinations were more or less nominal, and a degree of Doctor of Medicine, with the undisputed right to practice, could be secured after one year of study. At this low point in the progress of our profession, President Eliot made a significant statement: "The whole system of medical education in this country needs thorough reformation." Following this critical postwar period our schools improved more progressively, and the year 1870 marks the beginning of our modern era of medical education. From this date progress was also more rapid in the general field of education. According to studies at Harvard University in 1945, the population of the United States about tripled from 1870 to 1940, but in this same interval the enrollment in our high schools multiplied about ninety times and that in our colleges about thirty times.

In the second half of the nineteenth century, changes were taking place in Germany and in Central Europe which were to have a profound influence upon medical science and education in America. German medical science of the first decades of the nineteenth century was still greatly inhibited as the result of the Napoleonic Wars and by the racial and political disunity which existed among the German States and principalities. It was, however, in the fourth and fifth decades of that century that Johannes Müller (1801-58) and his many gifted pupils initiated the real era of scientific medicine in Germany. The rapid advancement, in that important period, was stimulated by the nationalistic spirit of the time arising from an intense desire for "racial and political solidarity." Progress, therefore, became very rapid in German medical science after the revolution of 1848, the consolidation of the German states into the German Empire in 1871, and following the establishment of peace in central Europe through the military and diplomatic efforts of Bismarck. Thereafter the center of advanced training and inspiration in scientific medicine shifted to Germany and to central Europe in about the last three decades of

those desiring premedical education. The completion of the reconversion of our schools is made more urgent by the estimated postwar need of large numbers of doctors for the army, navy, and veterans' associations, and by the increased requirements of our civil population. With the end of the war serious financial problems are again arising in our medical schools due to diminishing government aid, lowered income from endowments, higher salaries to meet greater living costs, and enlarged pay rolls, as teachers return from the armed forces or from government service. Let us sincerely hope, if we are to have postwar military training, that it will be arranged to disrupt as little as possible the progress of our carefully planned peacetime medical education program.

Adequate premedical education is, as ever, a vital and much debated problem, and depends as much upon a wise choice of students of superior natural intelligence as upon their training. Unfortunately, it is in these important formative years that the medical student's education has been most often curtailed. The mere memorizing of large masses of facts and figures is not so important as that the student learn how to find and assemble them for himself, that he become able to grasp a problem quickly, think it through logically, and present his conclusion clearly to others. A university, moreover, has done little for a student which has not helped to formulate his conception of "right" and "wrong" from the "ethical" as well as from the "mathematical" point of view, and which has not called upon the natural enthusiasm of youth to develop his habits of work and his "latent initiative and talents," and which has not awakened in him an intense desire for knowledge and an ardent curiosity in every new step in his education. The physical, chemical, and biological sciences are intensely interesting and should never be allowed to appear dull or commonplace. This requires, however, individual and personal instruction, and is not easily accomplished by the more brutal methods of mass production in education. The premedical student will, of course, need the so-called general tools of education: the ability to read, write, and speak the English language correctly, fluently and understandingly and, with these, a working knowledge of at least one foreign language. He will need, moreover, some specific tools for his education, such as mathematics, physics, chemistry, and general biology, which will enable him to comprehend more quickly the basic principles of his lifework for medical science is, after all, in great part, a very complex form of mechanical and chemical engineering, but in a biological setting. Cultural training, too, is important, for he is to be a member of society as well as a physician. He should, therefore, have some knowledge of the history of mankind, of his literature, of his art, of his economic and social life, of his philosophies and religions, of his achievement, and of the things and ideals for which man, through the ages, has been willing to work, to fight, and to die. It has been said that such things take too much time and are not needed by a medical student. It will, however, give him at least some comprehension of the broad expanse of human knowledge and of man's thoughts and desires. It will also give him a more sympathetic understanding of his fellow men; it will create in him a desire to elevate the standards of his profession; and most important of all, will enable him personally to sustain a broad general view of life while



field. The development of the proprietary schools was, perhaps, a natural and a necessary part of the early growth of America, but they were no longer comparable to the modern medical departments developing in a few of our endowed universities. From the beginning, too, they were unfortunate in often being motivated by selfish aims and in lacking the support and the inspiration and leadership which they might have had as respected departments in our institutions of higher learning.

Such were the rather meager results of the first three hundred years of hard and discouraging effort for the establishment of medical education and of medical practice in the formative period of America. As pioneers, however, we had cleared our fields, good seed had been sown, and we were prepared to reap the harvest in the form of better medical education and better medical care in a century of greater opportunity.

America, at the turn of the twentieth century, was experiencing the culmination of a change in its social life, influencing every aspect of man's individual and cooperative effort. These changes come chiefly as the result of developments in our economic and industrial life which furnished both the stimulus and the financial support for many forms of social progress. We found ourselves changing from a nation which had been predominantly rural to one that was more largely urban and industrial. We perfected the principle of mass production in our factories. We developed various and extensive means of transportation and communication. We discovered large quantities of raw materials and, through research in physics and chemistry, we were able to employ more scientific methods in industry. We developed new means of generating power and new and more rapid ways of manufacturing commercial products and of making new and useful synthetic substances. Urbanization and the new and convenient means of transportation and communication brought the people of different parts of America together and broadened their outlook upon life. Large fortunes accumulated in the hands of charitable men, and libraries, universities, and hospitals benefited thereby. Large varieties of "desirable commodities and services" were created which stimulated commerce and added to human comfort and happiness. Thus in the first part of the twentieth century, and more especially in the last twenty-five years, the people of Canada and of the United States have made rapid progress and, fortunately, medical science has also advanced, but it has been profoundly stimulated and aided by the social and economic changes taking place.

The medical profession of 1946 also has many important problems, social, political, economic, and educational, all modified by the war and its ending. The educational needs of our returning medical veterans are many, and they are being efficiently met. The postwar reconversion of our medical schools is gradually being completed. It is reliably reported that all but five will return to their prewar calendar in 1946, and the remainder in 1947. Our schools, at the moment, are handicapped by the lack of adequately trained premedical students, by the scarcity of teachers for the preclinical branches, and of nurses for our teaching hospitals, and finally, by the still uncertain military status of

cal specialties since this was written forty-two years ago. Our schools are better endowed, facilities for training are greatly increased and are well organized. More and more well-trained men are coming along. Twenty-six thousand have passed their specialty boards in all branches of medicine, and yet the number of qualified men is still entirely inadequate to meet our growing needs. In Canada, as well as in the United States, this is true, especially in the smaller cities with their nearby rural communities, where a much larger percentage of the total amount of our major obstetrics, gynecology, and abdominal surgery than is generally realized is still in the care of inadequately trained men. Weir Mitchell had a saying which may emphasize the importance of this point. It runs as follows: "The rate of advancement in medicine is to be tested by what the country doctor is."

In the past, extensive changes in the fundamental ways of training our youth have been adopted very gradually. The war, however, has aroused an intense activity in the study of basic educational questions and of plans for the future development of our liberal arts colleges and universities. The educational literature has been actually flooded with articles and books upon these fundamental problems written by professional educators, by specially appointed committees from nearly all of our institutions of higher learning, and by members of organizations interested in this field of science. Plans are on foot in many of our colleges and universities to experiment with radical new ideas and to adopt drastic changes in their curriculums. We are already beginning to feel the impact of some of these revolutionary ideas in our medical schools.

Today we are living in an age of intense research activity. It is common practice in every phase of our social, professional, and industrial life. It has had a profoundly vitalizing influence upon our national life, and has been largely responsible for the social and industrial changes which have been taking place. Fundamental research, however, had its inception and was nourished in the laboratories of pure science in our universities, where generations of devoted men have labored for years on the basis of intellectual interest rather than personal gain. The profound and yet practical nature of the accomplishments of these men is, today, deeply impressed upon the minds of this generation through the spectacular and vital help which our universities were able to give to our war effort.

Modern medical research may be said to date from the year 1543 when Andreas Vesalius published his treatise, *De Fabrica Humani Corporis*, containing almost the first important advancements in anatomic knowledge since the death of Galen in A.D. 201. His work came at the end of the "dark ages" in medicine when authority had ruled supreme and men's minds had not been free to think and express themselves independently. The seventeenth century, which followed, was one of intense and brilliant anatomic research carried out by men whose names are familiar to us all in the pages of our books of anatomy. In this century the science of physiology had its birth and chemistry was not yet fully differentiated from alchemy. William Harvey, who was born in 1578 and active early in the seventeenth century, is generally considered

he must concentrate his energies upon the more narrow and more limited fields of medical science and practice.

The medical school curriculum has always changed from year to year to make room for new learning, but the modifications during the war have been chiefly adjustments to military necessity rather than permanent "advancements or improvements." The growing magnitude of the great mass of medical knowledge has required a constant search for methods by which a student may acquire a reasonable comprehensive but well-integrated and correlated course in the allotted time of four years. This has required careful interdepartmental cooperation in our schools with the elimination of much useless detail and a discriminating selection of that which should be taught. There is a growing tendency among professional medical educators to try out new methods. They would limit somewhat the teaching of the different branches of medical science as independent separate subjects, and would have the entire four years of the medical school curriculum made up of carefully integrated and correlated courses with the various phases of each course presented by teachers from different departments. Under this system fewer hours would be devoted to anatomy, physiology, and biochemistry as independent branches of science and more time to their study, as, correlated by nature in tissues, organs and physiologic fluids, they each play their part in the structure and the functioning of the body in health or in disease. Experimental physiology and experimental biochemistry with their many subdivisions, likewise, have become too complex and intricate to be extensively studied as independent sciences. The established knowledge, however, which workers in these fields have developed, is of great value and the student should know its significance and its limitations and should become familiar with its application in clinical diagnosis and treatment. Clinical instruction is being instituted earlier in the medical course and the time honored teaching of large classes by lectures is slowly giving way to the clinical clerkship system in which the student is a respected and active member of a small group responsible for the diagnosis and treatment of clinical cases. The relation of teacher and student is becoming more intimate, instruction is being imparted in smaller groups and visual methods of presentation are being used more and more.

Our intern service of one or two years supplements the clinical instruction of our medical schools and forms the foundation for general practice or, with certain modifications, for the medical and surgical specialties. It is well organized in our university hospitals but very much still needs to be done to develop the intern training program in our independent hospitals.

The modern conception of a graduate program for advanced training in the surgical specialties is less universally established than our intern system. It was making a small beginning in a few of our universities as early as 1900. In 1904, in his Yale address Halsted wrote: "Although we now have in the United States several (five or six) moderately well endowed medical schools with university connections, yet the problem of the education of our surgeons is still unsolved. Our present methods do not by any means suffice for their training." Much has been done for advanced graduate training in the surgi-

would interfere with the rapid, free, and unhampered progress which medical science and education have made in recent years.

As a profession, we have carried more than our share of the treatment of the indigent, but we have not always fully realized the plight of the very large low income group whose earnings cannot cover the cost of a major or prolonged illness. Therein lies much of the cause of the predicament in which we find ourselves today. These people are aware of the desirable and valuable services which modern medicine has made possible and they are anxious for a plan which will place these services within their reach. In this they are encouraged by organized labor, by a socially minded group in our federal government, and most of all by the medical profession. The only difference of opinion lies in the method by which these services are to be obtained. As a profession, we are not unlike an industry which has developed a desirable and much needed product but has given too little thought to a method of marketing it. We have lacked a sales department to devise a mutually satisfactory and workable plan by which this low income group could obtain adequate medical services under our American system of free enterprise.

Medical men, like other scientific groups, are naturally inarticulate on political matters. As long, however, as we choose to isolate ourselves from such things and remain politically impotent we must not complain if others, with less understanding and with less experience with medical problems, think and act for us. As in the early days of our Republic, the medical profession of today might make more effort to gain the respect and the confidence of Congress. As members of that body more of us might become good statesmen, and on occasion, shrewd but honest politicians. The protection of the health of a nation is one of the most important functions of Congress, but unfortunately, often the most neglected. We must, of course, strenuously oppose any form of arbitrarily or bureaucratically controlled medical practice. Nevertheless we must take a positive stand. We cannot forever remain merely a party of the opposition for, let us make no mistake, this rising demand of our people for fuller medical care is a challenge to our profession which will not be denied. No matter how this challenge is met, the undertaking is going to be a large one which can be accomplished only by closer cooperation between our government and our profession than exists today. With these two forces working honestly and wholeheartedly together, it will be possible to develop a workable plan, suitable to all concerned, which will not destroy the self-respect nor the freedom of action of our profession. Whatever the outcome of this controversy in the United States, however, and whatever effect it may have upon us personally, we should remember that it is our sacred and sworn duty to work unselfishly for the best interests of the American people. If we do not do this we shall deserve to lose the confidence and the respect of the public which we have gained through many generations of hard, unselfish work.

With your indulgence, may we discuss some matters relative to our own association? Since the beginning of the war we have missed two of our annual meetings and three of our midyear meetings. While poetically, Thomas Haynes Bayley (1797-1839), an early English song writer and author, may

one of the most accomplished individual research workers in the whole history of experimental science. He was a great genius, not because, as an efficient technician and observer, he had many important isolated discoveries to his credit, but for the reason that he was a man of imagination, a deep thinker, and accustomed to meditate upon and to speculate about his scientific findings. It is known that his treatise, *De Motu Cordis et Sanguinis*, was not published until after at least nine years of thoughtful and laborious study and experimentation. His greatness was also in his intellectual ability to take a broad general view of a subject under investigation, to use simple, practical methods of proving the elements of his problems and, finally, to establish fundamental facts and guiding principles which, through the years, have been the basis for immense advancement in medical science. It was with this quality of mind that William Harvey was able to prove the circulation of the blood and to open to our consciousness that great highway which carries the essentials of life to every organ and to every cell in the body.

Modern medical education is inseparable from research activity. Through their union we have reaped a rich harvest of technological advancements in medical science and have created a sphere of endeavor where the principles of the basic sciences, of pathology and clinical medicine, and those of logic and common sense are brought together to solve the practical problems of medicine. The very spirit of research activity in our schools has stimulated the interest and the enthusiasm of both the teacher and the student in their everyday work, and has awakened their curiosity in the new facts and in the unsolved problems of medicine. They are no longer satisfied merely to "saturate" themselves with old established knowledge. It has also developed habits of precision, of careful direct observations, and of critical appraisal of collected evidence which are invaluable in medical practice as well as in the laboratory. Research has thus become an important and a vitalizing influence in medical education.

As a profession we are rather proud of the rapid advancements we have made in medical education and medical science in America. In the United States, however, we are somewhat alarmed by the powerful political and social pressure being brought upon us for radical changes in our methods of medical practice. It is necessary that we realize the importance of this situation. It is a problem of utmost concern to our people and to our profession. It is fundamental and should be settled only after most careful consideration. In the final analysis, no solution will be satisfactory to our people which does not follow the principles of our American way of life. We need, therefore, to face this situation honestly and intelligently, but we must be forceful enough and resourceful enough to maintain the position of leadership in the medical care of our people which the medical profession in a free country should occupy.

For years we have talked much about federalized medicine. It has been the opinion of the majority of our profession that governmental regimentation and political control of the practice of medicine would stifle initiative, would cause a deterioration in the quality of the services rendered the public, and

papers and holding a few separate simultaneous sessions; one for papers purely obstetric and the other for those devoted entirely to gynecology and related surgery? Papers of interest to both groups could be presented by joint session as at present. This would make possible a larger and more diversified program to suit the special interests of each member, would increase the size and importance of our transactions, and would better repay us for the not inconsiderable expenditure of time and money incurred in attending our meetings.

In the constitution of our association it is stated: "Its object shall be the cultivation and promotion of knowledge in whatever relates to obstetrics, gynecology, and abdominal surgery, except that which is peculiar to the male." In recent years, as the specialties have become more sharply defined, this has, by common consent, been interpreted, if one can express the unwritten law accurately, to include only such abdominal surgery as is closely and necessarily related to obstetrics or gynecology. In this we have followed the trend of the times. It may be rightly said that obstetrics is probably the oldest specialty and, combined with gynecology and related abdominal surgery, one of the largest, also that there is thus formed a natural specialty, limited to one sex and circumscribed by a common anatomy, a common physiology, and a common pathology. Our specialty, moreover, has amply justified its existence by striking advancements in medical science and by gratifying improvement in clinical practice.

Are the specialties, however, as they exist in American medicine today, entirely independent of one another? Is any one of them a thing apart in medical science? Are they not all very closely related to each other and to the basic sciences and to the principles governing medicine and surgery? Our specialties are major divisions of medical science and each has many spheres of activity where knowledge of much value to other specialties is available. In the most orthodox practice of a specialty, we must often cross the strictly defined boundaries of other divisions of medicine or surgery. Is there not, therefore, an undesirable influence in what some are pleased to call overspecialization, with too sharp an interpretation of the lines between the specialties and too narrow a view of what each should include? Is it not one of the pitfalls of specialism to concentrate unduly upon limited fields in clinical medicine and to lose the stimulus and the broadening influence of contacts with other divisions of medicine? Is it wise to lose touch with the general body of medical knowledge and should we not hold fast to its guiding principles? It is, of course, true that, as medical knowledge within our specialties has become more complex, we have each individually been obliged to accept a more limited field of endeavor. The workers within a specialty, however, comprise a whole group of men with widely varying activities within the separate departments of their specialty. The combined interests of such a group are much broader than those of an individual and will be found to cover not only every phase of their specialty but also all knowledge related to it.

The application of these thoughts to our own association would seem to be, that we should have as broad a general policy as possible within the bounds of our constitution as now interpreted. It would also mean that we should

have been correct when he wrote in his poem *The Isle of Beauty*: "Absence makes the heart grow fonder," yet practically in medical organizations, interest thrives upon frequent meetings, excellent programs, and good fellowship. It would seem appropriate, therefore, as we gather in this immediate postwar period, after so many interruptions in our professional life, that we should pledge renewed support to every phase of our organized effort and give careful consideration to ways and means of improving our association and of making it as effective and influential as possible.

In 1888, when this association was founded, the population of Canada and of the United States was smaller than at present. Today, not only is the population of our two countries larger, but, with better and more extensive educational facilities, the number of men more thoroughly trained in our specialty has become relatively greater. Should we not, therefore, along with other organizations in our specialty, give careful consideration to deserving members of this group and, as they gain experience and show their worth, make room for them in larger numbers in our obstetric and gynecologic organizations? For some years the membership of our association has averaged about one hundred and thirty and, with the addition of four or five new men each year, it has remained nearly stationary. This has made our meetings very companionable and our fees have about met our expenses. Would this, nevertheless, not be an opportune time to increase our membership more nearly to our constitutional limit of one hundred and fifty Fellows? More room might be made for new members and our ranks closed for more active participation in our programs, by enforcing more strictly paragraph XI of our by-laws relating to attendance. The scope of our future programs, moreover, might be broadened if new men were selected with as diversified special interests as possible within the bounds of obstetrics, gynecology, and related surgery and also if the number of men in our whole association, primarily interested in one or the other of the two major divisions of our specialty, were fairly evenly divided.

The scientific programs of any medical organization are, of course, necessary to its success. If these programs are not of enough volume nor sufficiently diversified to meet the special interests of each member, some will tend to lose interest and drift away. For some years the programs of this association have consisted of about nineteen papers. Four of these are usually presented by invited guests. One is the Foundation Prize Thesis, and one the president's address. As a rule one or two of the papers on the program are not presented because the members are unable to attend the meeting. The remaining eleven or twelve scientific papers thus presented by our Fellows do not seem a very large volume of work for an organization of one hundred and thirty members. Some years ago many more papers were presented, as our older transactions show. This was accomplished, however, by holding long morning, afternoon, and evening sessions. It was a tiring experience and gave little time for recreation or for members to become acquainted. Would not, however, some method of increasing the volume of our work be of value to our Association? Could this be accomplished, during the three days of our meeting, by classifying our



## PREGNANCY IN THE PATIENT WITH HYPERTENSIVE DISEASE\*

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WE HAVE thought it worth while to survey our experience with pregnancy in women with hypertensive disease. There are relatively few such studies based upon any considerable series, and in most studies extant there has been a selective factor in that therapeutic abortion has been done in the more severely hypertensive patients. It has not been our policy to abort such women, and our large material therefore offers an almost unique opportunity for the study of the natural history of pregnancy in hypertensive women.

### Material and Methods

We have selected from our toxemia files all women in whom recorded blood pressures before the twenty-fourth week of gestation permit the diagnosis of "hypertensive toxemia." In the thirteen-year period from the opening of the hospital in October, 1931, through 1944, there were 301 pregnancies occurring in 218 women, in whom the diagnosis of hypertensive disease could be established by this criterion. We have taken only those cases where (a) hypertension was known to have existed before pregnancy, or (b) hypertension was found before the twenty-fourth week of gestation, no previous normal readings having been recorded. Our standard for hypertension is 140/90 or greater. Patients showing hypertensive levels of blood pressure only at the initial clinic visit were excluded. Recognizable cases of glomerulonephritis and pyelonephritis were rejected; however, 15 patients (7 per cent of the series) were classifiable as "renal disease." We believe that these were either cases of nephrosclerosis secondary to hypertensive disease, or cases with superimposed pre-eclampsia.

Our postpartum toxemia clinic records have been of great value, in that they have given us repeated blood pressure readings while the patients were not pregnant. Also, we have looked through the record room files of every hospital in Hudson County, and whenever we found an admission of one of our patients—before or after she came into our hands—we have studied the hospital chart.

Renal function was assessed by Fishberg's simple urine concentration test,<sup>4</sup> and by the urea clearance. Blood and urine ureas were determined by Van Slyke's manometric urease methods.<sup>6</sup> Urinary protein was estimated by the sulfosalicylic acid method, and quantitative measurements were made by the procedure of McKay (Peters and Van Slyke<sup>6</sup>).

### The Patients

There were 194 white and 24 Negro patients, a ratio of 8:1. In all hospital admissions, the ratio is 18:1. At the time of the pregnancy in which the original diagnosis of hypertensive disease was made, they ranged in age from 16 to 44, with half in their thirties; the average age was 32½ years. Nearly one-fourth (66) were para 0, although 16 of these had had previous abortions; eight were elderly primiparas. Half of the patients were para iii or greater.

\*Presented, by invitation, at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.



adapt our scientific programs to meet the needs of workers in every phase of our specialty and be willing to include in these programs not only subjects of interest in every phase of obstetrics, gynecology, and related surgery, but also those subjects of special interest and value to our members which may arise in any field of medical science. This is not an argument against specialism but a plea for a broader conception of this extremely valuable trend in modern medicine.

World War I and, especially, World War II have caused a serious interruption or the utter destruction of the progress of medical science and education in many parts of Europe and Asia and in the world at large. It becomes the responsibility, therefore, of those of us living in areas less seriously affected to bear the torch of medical progress for the rest of the world. The burden of this responsibility will fall heavily upon the people of the British Commonwealth and upon the citizens of the United States. If, through lack of aggressive, intelligent, and cooperative effort or because of unwise leadership or the blight of bureaucratic control, we allow this torch to fall, the light of medical science will quickly fail and the people of the world will suffer a loss which will not be replaced for many generations. Is it not the responsibility, therefore, not only of our universities and of our medical schools but also of such educational groups as our own, to do all in our power to improve our organized efforts for the advancement of medical education and of medical science and practice? Is it not also our duty, as living members of our own revered association, to maintain the broad-minded, high standard of excellence set for us by the Founders of this Association and sustained for so many years by the fine Fellows who followed them?

TABLE I. SUMMARY OF PREGNANCY AND FOLLOW-UP FINDINGS IN 218 HYPERTENSIVE WOMEN HAVING 301 PREGNANCIES AT THE MARGARET HAGUE MATERNITY HOSPITAL

INITIAL SYSTOLIC BLOOD PRESSURE, MM. HG.:	140 TO 159	160 TO 179	180 TO 199	200 OR MORE	TOTALS
<i>Based upon pregnancies</i>					
Total pregnancies	123	92	43	43	301
First recorded blood pressure					
Prepregnant, cases:	28	32	16	15	91
First trimester, cases:	24	22	7	5	58
Second trimester, cases:	65	25	13	16	119
Third trimester, cases:	6	13	7	7	33
Proportion with midpregnancy drop in blood pressure (106 cases), per cent:	28.9	48.4	56.3	42.9	39.6
Blood pressure near delivery, compared with initial recording					
Lower, per cent:	1.8	31.5	36.8	40.5	20.8
Same ( $\pm 20$ mm. Hg.) per cent:	55.8	43.8	39.5	48.7	49.1
Higher, per cent:	42.4	24.7	23.7	10.8	30.1
Incidence of superimposed toxemia in 149 cases with prepregnant or first trimester blood pressure recordings, per cent:	28.9	27.8	30.4	30.0	28.8
Fetal mortality, per cent:	31.7	32.6	39.5	67.4	38.2

TABLE II. PROTEINURIA IN RELATION TO DEGREE OF HYPERTENSION (NEAR DELIVERY) IN 300 HYPERTENSIVE PREGNANCIES

SYSTOLIC BLOOD PRESSURE, MM. HG.:	140 TO 179	180 TO 199	200 TO 219	220 OR MORE	TOTALS
Total cases	187	64	33	16	300
Urine normal, per cent	66.8	36.0	12.1	0	50.7
Possibly significant proteinuria ("trace"), per cent	11.8	10.9	18.2	6.3	12.0
Significant proteinuria, per cent	21.4	53.1	69.7	93.7	37.3

week of pregnancy. She was a Negro woman 32 years of age, gravida ii, para i, estimated date of confinement, March 14, 1936. She weighed 177 pounds, with a gain of 21 pounds over the prepregnancy weight. Blood pressure 140/90, no proteinuria, no edema, and no complaints. One week later, she came in, in active labor, and delivered a living baby. The blood pressure in labor was 140/95, and was no higher during her hospital stay. On March 20, six weeks postpartum, the pressure was 190/120. She was seen many times subsequently, and the lowest nonpregnant pressure ever observed was 180/105.

We saw her in four later pregnancies, and frequently between all pregnancies. The nonpregnant blood pressures ranged from 180/105 to 280/160. In every pregnancy, except the fifth, which aborted at three months, the blood pressure dropped to low normal levels, and usually rose to 140-150/90-98 in the last month. All pregnancies but the fifth and sixth eventuated in live births. Within two weeks post partum, the blood pressure rose markedly after every pregnancy, and was never below 180/105. In February, 1940, she was admitted to the hospital for a workup, at which time she was ten months post partum. In eight days of bed rest, her pressure varied from 224/140 to 280/160. She had frequent severe headaches, vomiting, blurring of vision, and cardiac enlargement and insufficiency (generalized edema and dyspnea). The retinal arteries were tortuous and beaded.

In October, 1940, she again became pregnant for the sixth time, and had a cerebral accident at about the time of conception. We first saw her again when she was six months pregnant. Weekly blood pressure readings varied from 110/60 to 130/80, except for one of 170/120 obtained when hospitalization was

There had been 840 gestations prior to the pregnancy in which the diagnosis of hypertensive disease was definitely made. The uncorrected fetal loss in these earlier pregnancies was 292, or 34.8 per cent. This checks almost exactly with the data of Browne and Dodds.<sup>1</sup> Seventy-six per cent of the multigravidas gave a history of previous toxic pregnancy. The history was unknown in 23 per cent, and in only two cases were the previous pregnancies known to be normal.

The medical history, as given by the patients, revealed scarlet fever in 10 per cent, rheumatic fever in 9 per cent, diabetes in 1 per cent, pyelitis in 1 per cent, and hypertension antedating pregnancy in 60 per cent.

The family history, which we do not regard as reliable, was said to be positive for "heart trouble," "kidney trouble," "strokes," or diabetes in 66 per cent. Sixteen patients (7.3 per cent) had had mothers or sisters dying in childbirth.

Fifty of the patients had 47 sisters and 15 daughters who delivered here in 112 pregnancies. Toxemia, often "pure" pre-eclampsia, occurred in 34 (30.4 per cent) of these pregnancies. This is five times the incidence of toxemia in our hospital. The 47 sisters delivered 92 babies, with a toxemia incidence of 35.9 per cent. Of the sisters, 44.7 per cent had at least one toxic pregnancy. Only one daughter had a toxemia.

### The Pregnancies

*Blood Pressure.*—The height of the systolic blood pressure, either before pregnancy, or as found early in pregnancy, is shown in the first five lines of Table I. Where the initial blood pressure is recorded after the twenty-fourth week, the chart shows a physician's statement to the effect that hypertension had been found earlier.

The blood pressure often drops markedly in midpregnancy, as has been reported by Reid and Teel,<sup>7</sup> and others. There were 106 pregnancies, with sufficient data to compare repeated prepregnant or first trimester pressures with pressures observed in the second trimester. A decrease of more than 20 mm. Hg. was found in 39.6 per cent; the blood pressure drop exceeded 40 mm. in 11.3 per cent. No change (i.e., less than 20 mm. Hg.) was found in 50 per cent, and an increase of more than 20 mm. was seen in 10.4 per cent (see Table I, line 6).

Often the pressure rose again toward the end of pregnancy. We have comparative data for 163 pregnancies. In 52.7 per cent, there was not a significant change from the second trimester readings. There was an increase of more than 20 mm. in 44.2 per cent, and in 16.6 per cent this rise exceeded 40 mm. Only five patients (3.1 per cent) showed a blood pressure decrease in the last trimester. The distribution of blood pressures near term is shown in Table II.

Usually the patients whose blood pressures rose in the last trimester were the ones whose pressures had dropped in midpregnancy. Superimposed pre-eclampsia or eclampsia occurred in some patients, thus accounting for some of the late increases.

The data in Table I, lines 7, 8, and 9, indicate that in nearly half (49 per cent) of the patients the systolic blood pressure near delivery was about the same as before pregnancy or early in pregnancy. In 21 per cent it was lower, and in 30 per cent, higher. The higher the initial pressure, the larger is the proportion of patients showing drops in pressure. Also, the lower the original pressure, the larger is the proportion of patients who have marked rises near delivery. The diastolic pressures showed the same trends as the systolic.

CASE 1.—As an extreme and interesting example of the blood pressure reduction often seen in pregnancy, we cite the case of M. R., History No. 25403. Her first pregnancy, in 1934 and at another hospital, was complicated by an unclassified toxemia. We first saw her Jan. 30, 1936, in about the thirty-fourth

There is no relation between the incidence of superimposed toxemia and the prepregnant or first-trimester level of blood pressure (Table I, line 10). Nor, as Table III shows, is there any clear-cut correlation with the parity of the patient, although toxemia is somewhat more prevalent in primiparas. The incidence in para iv, v, and vi patients is about half that in the others. The age relation is about the same as that of the parity, as might be expected (Table IV). Superimposed toxemia is somewhat more common in the younger hypertensives.

TABLE III. THE SUPERIMPOSITION OF TOXEMIA IN RELATION TO THE PARITY OF HYPERTENSIVE PATIENTS CARRYING PAST THE TWENTY-FOURTH WEEK

PARA:	0	1	II	III	IV	V	VI	VII OR MORE	TOTALS
Total cases	57	51	39	25	23	14	13	41	263
Superimposed toxemia, cases	26	19	12	8	4	3	3	15	90
Toxemia incidence, per cent	46	37	31	32	17	21	23	37	34

TABLE IV. THE SUPERIMPOSITION OF TOXEMIA IN RELATION TO THE AGE OF HYPERTENSIVE PATIENTS CARRYING PAST THE TWENTY-FOURTH WEEK

AGE, YEARS:	LESS THAN 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45
Total cases	38	63	74	60	28
Superimposed toxemia, cases	18	23	19	22	8
Toxemia incidence, per cent	47	36	26	37	29

Nineteen of the hypertensive patients who also had eclampsia or pre-eclampsia have had pregnancies subsequent to the one in which the diagnosis of hypertensive disease with superimposed toxemia was made. Ten, or 53 per cent, of these later pregnancies were again toxic. However, three women aborted and two delivered at home. Excluding these, the incidence of recurrent toxemia would be 71 per cent.

Hypertensive patients not showing superimposed toxemia in one or more pregnancies may show it in subsequent ones. Thus, in 63 subsequent pregnancies observed in women initially escaping toxemia, 16 cases, or 25.4 per cent, were toxic. This incidence approaches the total incidence of 34 per cent for the whole series.

### The Labors

In the 301 pregnancies, two patients died before delivery. Thirty-four were sectioned, 28 before the onset of labor. In the remaining 265 cases (including abortions), onset of labor was spontaneous in 181 (including six who came to section), or 60.0 per cent of the series. Medical inductions were successful in 69 patients, and bag inductions succeeded in 21, two of which were therapeutic abortions. In combination with medical induction, the membranes were artificially ruptured in 44 successfully induced cases.

### The Deliveries

Including abortions, delivery was spontaneous in 244 (81 per cent). Twenty-one had forceps deliveries, and 34 (11.3 per cent) were sectioned. Two patients died undelivered.

### Fetal Outcome

In the 301 pregnancies analyzed, 186 babies, or 61.8 per cent, were discharged alive. There were eight early abortions (2.7 per cent), 38 late abortions

suggested. At the thirty-seventh week, the pressure rose to 150/98, and then in succeeding weeks fell to 140/86. She never had any edema, proteinuria, or complaints. At forty-one weeks (July 6, 1941), she came in, in active labor and in good spirits. While in the admitting room, she suddenly had a tonic convulsion and died within ten minutes. The urine obtained in the admitting room showed a two plus proteinuria. Blood pressure was unobtainable (shock). Autopsy showed a cervical tear extending up the wall of the uterus to the tube and ovary (she had never had a cesarean section). Other findings were: marked cardiac hypertrophy, nephrosclerosis, an old right capsular cerebral thrombosis, and the liver changes of eclampsia.

Renal function tests, repeated many times, were always normal. Two months before death, the urinary specific gravity was 1.026 and the urea clearance 108 per cent. Except for the last urine, she never showed more than a very faint trace of proteinuria in the five years of close observation.

*Proteinuria.*—In half of the 301 pregnancies, the patients never had more than a very faint trace of proteinuria. The other half showed pathologic amounts in varying amounts, but only as they approached term. Proteinuria was definitely related to the greater degrees of hypertension (Table II), as has been found by others. Of the 65 patients who had a proteinuria of 8 Gm. per liter or more, 78.4 per cent had systolic pressures above 180 mm. Hg.

*Renal Function.*—Tests of renal function were made in all but eight pregnancies. In the simple Fishberg test, the patients in 58.5 per cent of the pregnancies had urinary specific gravities of 1.022 or higher and, an additional 18 per cent concentrated to 1.019 to 1.021. Since nearly all patients were on a restricted salt intake, and often on a low protein diet as well, we believe that three-fourths of the patients thereby proved normal renal function. (See Chesley<sup>2</sup> for discussion of renal function tests during pregnancy.) Urea clearances were done in 194 patients, including all who failed to concentrate to 1.022. Urea clearances of less than 50 per cent were found in eight patients, 50 to 59 per cent in seven, and 60 to 69 in fourteen. If we accept 60 per cent as the lower limit of normal, then 15 patients, or 7 per cent of the series, had renal impairment.

*Superimposed Toxemia.*—Nine pregnancies, in eight patients, were eclamptic. As for pre-eclampsia, we find it difficult to decide in many cases whether or not to make the diagnosis. As mentioned above, nearly half of the patients in the last trimester show rises of more than 20 mm. Hg over the blood pressure level of midpregnancy, and half showed some degree of proteinuria. If, however, we require both a rise in blood pressure and proteinuria, or marked proteinuria alone, then only 81 pregnancies could be considered as pre-eclamptic. By this criterion (perhaps too strict), the incidence of superimposed pre-eclampsia and eclampsia would be 29.9 per cent, or in pregnancies carrying past the twenty-fourth week, 34 per cent. This figure is considerably below those of Reid and Teel<sup>7</sup> (63 to 70 per cent), Wellen<sup>8</sup> (86 per cent), Dexter and Weiss<sup>3</sup> (50 per cent), or Mussey, Hunt, and Sluder<sup>5</sup> (51 per cent), but higher than the 17.9 per cent of Browne and Dodds.<sup>1</sup> These last writers, however, found that 82 per cent of their patients showed some "exacerbation" of the disease, i.e., increased blood pressure, or proteinuria, or edema, or other signs and symptoms of toxemia. The estimated incidence of toxemia depends, of course, upon the diagnostic criteria.

Premature separation of the placenta occurred in 17 cases, or 5.6 per cent. Nine of these were associated with superimposed toxemia, giving an incidence of ten per cent in the toxemic pregnancies.

Since the superimposition of toxemia is of crucial importance, as will be shown later, we have sought for some indication as to which women might be more susceptible.

nancies where the patients concentrated their urines to 1.022 or higher, there were 30 fetal deaths, or 23.8 per cent. In the 82 pregnancies where the patients failed to concentrate as high as 1.022, there were 36 fetal deaths, or 43.9 per cent—nearly twice the rate in the former group.

Urea clearances were done in the patients who failed to concentrate to 1.022 or higher. There were 11 pregnancies in 11 patients, where the clearances were less than 70 per cent. Nine of the babies were lost, a mortality rate of 81.8 per cent—nearly three and one-half times the rate in pregnancies where the urinary specific gravities reached or exceeded 1.022.

*Superimposed Toxemia.*—In the nine eclamptic pregnancies, six babies were stillborn and two died in the neonatal period. The 81 pregnancies with superimposed pre-eclampsia gave rise to 44 babies that lived. There were 31 stillbirths and six neonatal deaths. Thus, the fetal loss in the 90 toxic pregnancies was 50 per cent. We may contrast the 173 pregnancies carrying past the twenty-fourth week and uncomplicated by superimposed toxemia; here the fetal mortality was 18.5 per cent—a little more than one-third the rate in the toxemic pregnancies.

*Fetal Weights.*—Once the fetus attains a weight of 2,500 Gm. its chances of survival do not seem to be improved materially by allowing the pregnancy to continue. The data in Table VI show no significant differences in the fetal mortality rates in the weight classes above 2,500 Gm. Apparently the hazards of neonatal death in the smaller babies are offset by the danger of stillbirth in continuing pregnancies. In all weight groups, the loss by stillbirth exceeds the neonatal mortality. There were 160 babies weighing more than 2,500 Gm. Of these, 12, or 7.5 per cent, were stillborn. Of the 148 live births three, or 2 per cent, succumbed.

TABLE VI. FETAL WEIGHTS AND MATERNAL BLOOD PRESSURE NEAR DELIVERY, IN RELATION TO FETAL MORTALITY\*

BIRTH WEIGHT:	WEIGHT UNKNOWN	LESS THAN 1,000 GM.		1,001 TO 1,500 GM.		1,501 TO 2,000 GM.		2,001 TO 2,500 GM.		2,501 TO 3,000 GM.		3,001 TO 3,500 GM.		3,501 GM. OR MORE	
		CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)
SYSTOLIC BLOOD PRESSURE, MM. HG															
Less than 180	3	27	100.0	8	87.6	13	38.4	12	18.3	29	6.9	49	2.0	46	4.3
180 to 219	10	18	100.0	14	57.2	9	55.6	11	27.3	10	20.0	10	20.0	8	25.0
More than 220	3	6	83.3	1	100.0	5	100.0	0	-	4	0.0	5	40.0	0	-
Totals	16	51	98.1	23	69.6	27	55.6	23	17.4	43	9.3	64	9.4	54	7.4

\*There were 16 cases, all deaths, with no recorded weights; nearly all less than 1,000 Gm.

### Sterilization and Therapeutic Abortion

Twenty patients were sterilized, twelve at the time of section, and eight post partum. Three therapeutic abortions were done. One patient with malignant hypertension died six weeks after the abortion. Another patient, a rather mild hypertensive, succumbed to a cerebral hemorrhage six years and four months later. The third patient is still alive fourteen years later, having borne a living child in the interim.

### Immediate Maternal Mortality

There were six immediate maternal deaths, an incidence of 2.0 per cent, or almost ten times the rate for the whole hospital experience. Four of these deaths

and previable prematures (12.6 per cent), 53 stillbirths (43 antepartum and 10 intrapartum; 17.6 per cent), and 16 neonatal deaths (5.3 per cent).

Since the hypertensive mother's chance for a living baby is a practical consideration, we have analyzed some of the factors associated with fetal loss.

*Initial Blood Pressure.*—The data in Table I, line 11, show that the higher the initial pressure, the greater is the fetal mortality. Browne and Dodds<sup>1</sup> had 25 patients in whom the initial blood pressure was 150/100, or more. Only eight (32 per cent), had living babies, and no patient with an initial systolic pressure greater than 180 bore a living child. In our series, 31 women were known to have prepregnancy pressures of more than 180; 16 of these had living babies. Of 75 women with prepregnancy systolic pressures of less than 200, four out of five had living babies. One patient, three years post partum and two years before conception of the pregnancy analyzed, consistently had a pressure of 210/120 to 220/130 over several months of observation. She was seen in the eighth week of gestation, with a pressure of 210/128, which she maintained. Pregnancy was allowed to continue until the twenty-eighth week, at which time it was interrupted because severe pre-eclampsia had supervened. A 790 Gm. child was born, and it lived.

*The Midpregnancy Blood Pressure.*—A rise in blood pressure during the second trimester is most ominous for the fetal prognosis. There were 106 patients whose second trimester blood pressures could be compared with earlier readings. In the 11 patients showing midpregnancy rises in pressure, only one (mentioned above) had a living baby; thus the fetal mortality was 91 per cent. In 53 patients whose blood pressure remained constant (within 20 mm. Hg), the fetal loss was 28.3 per cent. The mortality was 21.4 per cent in the 42 cases where the maternal blood pressure dropped in the second trimester.

*Blood Pressure Near Time of Delivery.*—The higher the blood pressure near delivery, the greater is the fetal loss. In analyzing the times of fetal death, we unexpectedly found that only neonatal deaths increase regularly with increments in the hypertension. Table V summarizes the relation of the blood pressure to the fetal outcome. Apparently our more severe hypertensives did not have a tendency to abort spontaneously.

TABLE V. THE BLOOD PRESSURE NEAR DELIVERY IN RELATION TO THE FETAL OUTCOME IN 301 HYPERTENSIVE PREGNANCIES

AVERAGE SYSTOLIC BLOOD PRESSURE, MM. HG	CASES	DIS- CHARGED LIVING (PER CENT)	EARLY ABORTION (PER CENT)	LATE ABORTION AND PREVIALBLE (PER CENT)	STILLBIRTHS		NEONATAL DEATHS (PER CENT)
					ANTE- PARTUM (PER CENT)	INTRA- PARTUM (PER CENT)	
140 to 159	108	81.5	0.9	7.4	6.5	1.8	1.8
160 to 179	75	64.0	2.7	16.0	9.3	5.2	2.7
180 to 199	61	45.9	6.6	11.4	27.8	1.6	6.6
200 to 219	33	45.5	3.3	18.2	15.1	9.0	9.0
More than 220	24	29.2	0.0	20.8	29.2	0.0	20.8
Totals	301	61.8	2.7	12.6	14.3	3.3	5.3

*Proteinuria.*—The appearance of proteinuria is unfavorable for the fetus. In the patients showing only insignificant amounts, or no proteinuria, the fetal loss was 31 per cent. With pathologic degrees of proteinuria up to 4 Gm. per liter, the fetal mortality was 40 per cent. Greater degrees of proteinuria carried a fetal death rate of 56 per cent.

*Renal Function.*—In assessing the role of renal functional impairment in fetal loss, we have excluded cases with superimposed toxemia. We do this because: (a) superimposed toxemia increases the fetal mortality, and (b) such toxemia may depress the urea clearance somewhat. In the 126 nontoxic preg-



### Discussion

Our analysis of the 301 hypertensive pregnancies certainly establishes the dangers of pregnancy itself—one woman in 23 died either immediately or within four months after delivery, and two in five lost their babies. The total maternal mortality was 20 times that for the whole hospital experience, the fetal loss was increased nearly tenfold, and the incidence of toxemia was multiplied by seven.

Of the 13 immediate and late puerperal deaths, four were uremie, and it is quite possible that pregnancy may have accelerated the renal decompensation. However, one of these deaths occurred six weeks after a therapeutic abortion done at sixteen weeks. In another case, there was some evidence of the onset of malignant hypertension before conception. The other two patients were not seen until late in pregnancy, at which time their urea clearances were less than 30 per cent. The times of onset of the malignant phase of hypertension are unknown in these two cases, although both had had severe hypertension two and three years, respectively, before conception.

Taking the 13 deaths together, eight were probably associated with the hypertensive disease, while five were attributable to intercurrent causes.

While pregnancy very definitely jeopardizes the hypertensive woman, the hazards are not great in two out of three cases. Two-thirds of our patients escaped superimposed toxemia. In this group, there were no immediate maternal deaths, and one of the two late puerperal deaths was of intercurrent causation. The fetal loss was 18.5 per cent. Among the one-third of patients who had pregnancies complicated by the superimposition of toxemia, there were six immediate maternal deaths (6.67 per cent), and five late puerperal deaths, giving a total maternal mortality of 12.2 per cent—ten times that in the uncomplicated hypertensive group. The fetal loss was exactly 50 per cent—almost three times that in the cases escaping superimposed toxemia.

If only we could determine which patients would escape pre-eclampsia or eclampsia, a good prognosis for pregnancy could be offered to two out of three hypertensive women. If the toxemia *causes* the damage done, then the prompt termination of a hypertensive pregnancy at the first sign of developing toxemia should protect the patient. If this were so, then perhaps any hypertensive woman could be given a chance at pregnancy, should she desire it. While her risks would be greater than those of a normal woman, there is a good chance that close supervision would give her a living baby.

The fetal loss of 38 per cent is greater than the mortality reported by Reid and Teel<sup>7</sup> (21.9 per cent), or by Browne and Dodds<sup>1</sup> (16.2 per cent). However, Browne and Dodds' standard for hypertension was 130/70. Wellen<sup>8</sup> recorded a stillbirth incidence of 36.2 per cent, and Mussey, Hunt, and Sluder<sup>5</sup> found a fetal loss of 30.6 per cent.

The midpregnancy drop in blood pressure has a very practical importance for diagnosis. An appreciable number of our hypertensives had perfectly normal blood pressures over several weeks of the second and third trimesters. Had their earlier hypertensive pressures been unknown, they would be classifiable



occurred in the first pregnancy definitely established as hypertensive, while two died in later pregnancies. Briefly, the deaths may be summarized as follows:

1. N. W., History No. 1812. Negro, aged 41 years, gravida xi, para x, previous pregnancies toxie. Nonpregnant blood pressure in 1936, 162/92 to 170/100. Admitted Aug. 3, 1937, in thirty-fifth week of pregnancy, in labor and bleeding. Blood pressure 194/120, marked edema. Sectioned for severe abruptio placentae; baby stillborn. She was anuric for four days, but established a good diuresis. Died on the twelfth postoperative day, of peritonitis. No prenatal care.

2. B. H., History No. 34990. Negro, aged 21 years, gravida i, para 0. At four months gestation, blood pressure 240/150, no proteinuria, no edema, no eye-ground changes. One month later she developed edema, blurring of vision, retinal hemorrhages and exudates, and proteinuria known to be of acute onset. Blood pressure had remained nearly constant. She aborted spontaneously at twenty-three weeks, and died on the fifth postpartum day of a pulmonary embolus. The patient's mother had died in childbirth, cause unknown.

3. E. M., History No. 36091. White, aged 41 years, gravida x, para ix. She was sent to the hospital on Oct. 11, 1938, after six convulsions, by a local physician who stated that her blood pressure had been 220 from early in pregnancy. She at once delivered a seven-month stillborn baby, and died the following day of circulatory failure incident to eclampsia.

4. M. B., History No. 21739. White, aged 36 years, gravida vi, para iii. Eclampsia in 1927; hysterotomy in sixth month, for severe toxemia in 1928, mild pre-eclampsia in 1935, nonpregnant hypertension (140/92) in 1936, severe toxemia in 1938 (another hospital), early abortion in February, 1939. Admitted in labor, in twenty-ninth week of gestation, Dec. 24, 1939. Blood pressure 170/138, 4 plus proteinuria, marked edema, and the whole train of severe toxemic symptoms. She had many petechial spots on her face and hands. There were old and new retinal hemorrhages. She delivered a stillbirth the same day, and died on the eighth postpartum day of bacterial endocarditis and anuria. No prenatal care. Her mother had died in childbirth, cause unknown.

5. E. P., History No. 32643. White, aged 23 years, gravida ii, para i (stillbirth with hypertensive toxemia included in this series). Nonpregnant hypertension, 185/120 to 220/130. A private patient, admitted Nov. 6, 1940, in seventh month of pregnancy. Blood pressure 250/150, proteinuria 3 Gm. per liter (of very recent onset), and no complaints. On the ninth day of bed rest, she had a fatal cerebral hemorrhage, and died undelivered.

6. M. R., History No. 25403. See Case Report. Died of hemorrhage incident to a rupture of the uterus while in early labor. Negro, aged 34 years.

### Late Puerperal Deaths

There were seven late puerperal deaths, occurring from six weeks to four months post partum. Four of these were uremic deaths in malignant nephrosclerosis, at the ages of 28, 31, 32, and 42 years. They were post partum six weeks (following therapeutic abortion), three months, four months, and ten weeks respectively. Another patient, who had long-standing rheumatic heart disease, died of "acute endocarditis" three months post partum, aged 32 years. One died of acute ventricular failure six weeks post partum, aged 36 years. The last one died nine weeks after the delivery of her fourth hypertensive pregnancy, aged 28 years. She had laid down for a nap, and was found dead.

All late puerperal deaths are known to be included here, since we have traced every patient to 1946.

## MORBIDITY ASSOCIATED WITH INDUCTION OF LABOR\*

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SINCE the causative factors of the onset of labor are still unknown, caution should be noted in evaluating any procedure which seems to have precipitated labor. For example, about 5 per cent of the patients hospitalized for inductions at St. Louis Maternity Hospital went into spontaneous labor before any procedures were carried out.

Hamblen<sup>1</sup> states that we do not know why labor begins. Reynolds<sup>2</sup> believes that the onset of labor is due to alterations in estrogen-pituitary-progestin balance influenced by uterine distention.

The most helpful work comes from Lyon<sup>3</sup> in his search to find changes concurrent with the initiation of labor. By using the new glucuronic acid method, the NaPG excretion in the urine decreases preceding the onset of labor similarly in those cases at term, postmature, and in premature groups. There is a positive correlation between an extensive fall of conjugated pregnandiol and the onset of labor. Also, there is strong evidence of a marked drop in available progesterone preceding the onset of normal labor.

With this new knowledge available, a different interpretation may be placed on studies of induced labor. Lyon<sup>3</sup> shows there is a 58 per cent decrease of sodium pregnandiol glucuronidate excretion in the urine during the four days before delivery takes place. The greatest changes take place within the 48 hours to 72 hours preceding termination of the third stage of labor.

Morton<sup>4</sup> of Lynch's Clinic reports induction of labor by means of artificial rupture of the membranes, castor oil and quinine, and nasal pituitrin. Guttmacher,<sup>5</sup> in 1931, and Slemmons,<sup>6</sup> in 1932, report further on induction of labor by means of artificial rupture of the membranes, showing that the latent period and duration of labor are shorter whenever the cervix is dilated, and naturally effaced at the time the membranes are ruptured artificially for induction of labor. Stern,<sup>7</sup> Plass,<sup>8</sup> and Mathieu and Holman<sup>9</sup> all show the low morbidity and excellent results obtained by induction. It must be remembered, however, that their material was selected from abundance and that their skill and working conditions were of the best.

In 1925 a unit history system was started at Barnes Hospital. This enabled a review of obstetric cases with their subsequent admissions to Barnes Hospital to be made. For this reason, and because of intern experience with many of these cases, the author chose to review all inductions from June, 1925, to July, 1927, at Barnes Hospital. This series constituted 160 cases, and the material was limited to only viable babies at the onset of the induction. No cases were taken under thirty-six weeks' gestation, and for the most part the elective rupture of membranes was used but rarely. Incidence of induction

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as pre-eclampsia, since they had acute rises in pressure after the twenty-fourth week of gestation, earlier known pressures having been normal. This factor confuses the interpretation of permanent hypertension apparently left as a sequel of "pre-eclampsia." Prepregnant blood pressure recordings in such cases are rarely obtainable, and the diagnosis of pre-eclampsia must depend upon readings taken during pregnancy—usually in the latter half.

### Summary and Conclusions

From the opening of the hospital in October, 1931, through 1944, there were a total of 218 patients in whom recorded blood pressures establish the diagnosis of "hypertensive toxemia," as defined by the American Committee on Maternal Welfare.

A detailed analysis has been made of the 301 pregnancies in which these patients have been seen.

The gross fetal loss: In prior pregnancies, 35 per cent; in first hypertensive pregnancy, 38 per cent; in subsequent pregnancies, 40 per cent.

Of 47 sisters of these hypertensive patients, who delivered here, 45 per cent had at least one toxie pregnancy.

Nearly 40 per cent of the hypertensive patients showed drops in the blood pressure in midpregnancy.

Proteinuria of some degree occurred in half of the pregnancies.

Renal function was normal in 93 per cent of the pregnancies.

Premature separation of the placenta occurred in 5.6 per cent of the pregnancies.

— Fetal loss increased with: higher initial blood pressure, second trimester rises in blood pressure, higher pressures near delivery, decreased renal function, proteinuria, and superimposed toxemia.

There were six immediate maternal mortalities (2.0 per cent), and seven late puerperal deaths. Thus the mortality was 20 times that of the whole hospital experience.

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TABLE

	MORBIDITY GRAV. I 41 % INCIDENCE 33½%			MORBIDITY GRAV. II PARA. I 15%			MORBIDITY GRAV. II PARA. 0 35%		
	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED
1925-26-27 (160 cases) Series	6	14	13	16	22	3	1	3	4
1928-34 (140 cases) Selected	8	10	34	16	7	6	4	3	2
1943 (50 cases) Selected	47	13	21	38	8	10	3	1	2
1944 (150 cases) Series									
Total (500 cases)	Green 61	Yellow 37	Red 68	Green 70	Yellow 37	Red 19	Green 8	Yellow 7	Red 8

226 Green—No Morbidity

146 Yellow—Morbidity not caused by induction of labor

372

128 Red—Morbidity, Maternal and Fetal, incurred by induction of labor

Combined Maternal and Fetal Morbidity 25%

10.6% of hospital admissions induced, parturients of more than 36 weeks' gestation

tion, as in the other two groups. Incidence of induction was 10.2 per cent of parturient hospital term admissions for the private service; 0.8 per cent for the ward service. This series comprised 150 cases. The combined maternal and fetal morbidity was 20 per cent. Fifty additional cases were selected from a 1943 group of patients, taken largely from a controlled private service, and induced by elective rupture of the membranes and pituitary extract, only if needed. The combined maternal and fetal morbidity was 8 per cent. This gave a total of 500 cases in all, which were subjected to critical analysis by obtaining the following information from each case.

Each case was then studied as to its morbidity. A green, a yellow, and a red marker were used to denote—no morbidity; morbidity, but not likely due to the induction of labor; and red indicating morbidity, thought to be caused by the induction of labor. This first general classification showed 226 green cases with no morbidity, 146 yellow cases with morbidity not caused by induction of labor, for example, acute upper respiratory infections, gastrointestinal disturbances, unexplained antepartum fever, etc. were listed. There were 128 red cases which made a maternal and fetal morbidity of 25 per cent for the 500 cases studied. Fetal morbidity, such as intracranial injury, still-born, when a fetal heartbeat was noted at the beginning of labor, and prolapsed cord, were included in these 128 red cases. However, fetal death from erythroblastosis or icterus neonatorum was not counted as morbidity and was classed as either green or yellow. The standard of morbidity was 100.4° F. or 38° C. for any two consecutive days of postpartum hospital stay, and was a minimum basis for classification as a red case. Postpartum hemorrhage, 500 c.c. to 700 c.c. plus; ruptured uterus, deep cervical and parametrial laceration, separation of the symphysis, and damage to bladder or rectum also

was 8.3 per cent of parturient hospital admissions of at least thirty-six weeks gestation. The combined maternal and fetal morbidity was 20 per cent.

The St. Louis Maternity Hospital cases from the years 1928 to 1934, inclusive, were chosen for the second group of induction of labor. These 140 cases were not a series, but a selection, chosen to show the morbidity associated with combining the older technique of pituitary extract, castor oil, quinine, bags, and bougies, with the addition of artificially rupturing the membranes as an added procedure when failure to induce occurred. Incidence of induction was 13.5 per cent of parturient hospital term admissions. The combined maternal and fetal morbidity was 40 per cent.

The third group of cases comprised all the inductions for the year 1944 at the St. Louis Maternity Hospital. No cases were taken under 36 weeks gesta-

History number	3rd Stage
Age	Date
Gravida	Hour
Paragravida	Duration
Complications:	Bleeding
1st Trimester	Ergot-Infundin
2nd Trimester	Placenta-Schulze-Duncan
3rd Trimester	Total hours of labor
Estimated date of confinement	Anesthetic
Date admitted for induction	Description of delivery
Urine	<i>Condition of Baby at Birth</i>
Blood pressure	Spontaneous cry
Weight gained	Spontaneous respiration
Weight on admission	Tracheal catheter
Fetal position, size in cm.	Medical respiratory and
Indications for induction	cardiac stimulants
<i>Induction of Labor</i>	Hot and cold baths
Started	Cyanosis
Date	Pallor
Hour	Twitching
Castor oil	Birth weight
Castor oil, quinine	<i>Maternal, First 14 Days of</i>
Ruptured membranes, spontaneous	<i>Puerperium</i>
or artificial	Temperature
Infundin	Average
Estrogen	Minimum
Ergot	Maximum
Bag	Catheterization
Bougies	Bleeding
Manual dilatation of cervix	Average
<i>Labor</i>	Moderate
1st Stage	Excessive
Date	Endometritis, acute
Hour	Date out of bed
Duration	Date discharge
Uterine contractions	Total hospital days
Sedation	Total postpartum days
Infundin	<i>Postpartum and Latent</i>
Presenting parts cervix	<i>Gynecological Complications</i>
2nd Stage	Condition of mother at time
Date	of discharge
Hour	Chronic subinvolution of uterus
Duration	Retrodisplacement of uterus
Uterine contractions	Cervical lacerations
Sedation	Cervicitis with erosion
Infundin	Condition of baby at time
Presenting parts cervix	of discharge
Date	Sequelae, comments
Hour of delivery	

TABLE II. GROUP 1; TOXEMIAS INDUCED  
(Which were 9% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		85%
	Mechanical induction	Bags	32%
		Bougies	15%
	Cesarean sections		0%
2. Average hours of labor and birth weights	Morbidity cases averaged		17 hours and 2,800 Gm.
	Nonmorbidity cases averaged		8 hours and 3,100 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		75%
	Nonmorbidity cases incidence		23%
4. Morbidity 44% combined maternal and fetal	29% Gravida—i	Maternal morbidity	30%
		Maternal mortality	0%
	15% Multipara	Fetal morbidity	14%
		Fetal mortality	14%
5. Latent sequelae	No lesions		14%
	Lesions		86%

Subsequent record on 53% of cases.

No subsequent record on 47% of cases.

*Diagnosis and Procedures:* Retrodisplacement of uteri; cervicitis with laceration; parametritis; complete hysterectomy; suspension of uterus; cauterization of cervix; conization.

TABLE III. GROUP 2; DISPROPORTION BETWEEN FETUS AND PELVIS, CONTRACTED PELVIS  
(Which were 6% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		71%
	Mechanical induction	Bags	16%
		Bougies	50%
	Cesarean sections		1%
2. Average hours of labor and birth weights	Morbidity cases averaged		32 hours and 3,200 Gm.
	Nonmorbidity cases averaged		9 hours and 3,200 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		80%
	Nonmorbidity cases incidence		40%
4. Morbidity 60% maternal and fetal combined	35% Gravida—i	Maternal morbidity	31%
		Maternal mortality	3%
	25% Multipara	Fetal morbidity	29%
		Fetal mortality	23%
5. Latent sequelae	No lesion		18%
	Lesion		82%

Subsequent record on 48% of cases.

No subsequent record on 52% of cases.

*Diagnosis and Procedures:* Retrodisplacement of uteri; cervicitis with laceration; parametritis; phlebitis; complete hysterectomy; cauterization of cervix.

The morbid cases had an average labor of seventeen hours, over twice the hours of labor in the nonmorbid cases, which averaged eight hours. Birth weights of the babies averaged 300 Gm. less in the morbid cases. Cervical laceration was acquired in 75 per cent of the morbid cases and in 23 per cent of the nonmorbid cases. Fetal morbidity and fetal mortality were the same, 14 per cent. Nonmorbid cases had more matured babies and were induced closer to the time of spontaneous initiation of labor.

The second grouping is that of "disproportion between fetus and pelvis; contracted pelvis." In 1925 to 1927 at Barnes Hospital, the series of 16 cases induced for disproportion between the fetus and pelvis is in contrast to an incidence of three cases induced in the larger series of 1943 to 1944 at the St. Louis Maternity Hospital. The use of Caldwell-Malloy x-ray pelvimetry, at or near the expected date of confinement, has furnished a more accurate means of classifying the pelvic disproportion to the particular fetal head under consideration. The use of the low cervical cesarean section with transverse incision (advocated by Phaneuf<sup>10</sup>) after a "trial of labor" rather than a "test of labor" has given such satisfactory results that this is now a method

MORBIDITY GRAV. III PARA. II 18%			MORBIDITY GRAV. III PARA. 0-I 19%			MORBIDITY GRAV. IV PARA. III 10%			MORBIDITY GRAV. IV PARA. I-II 25%			MORBIDITY GRAV. V+ PARA. III+ 19%		
GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED
13	16	5	5	3		5	5		2		2	4	10	4
6	2	9	3	1	3	1	7	2	2			8	5	5
18	1	1	5	4	2	2			2			11	1	
Green 37	Yellow 19	Red 15	Green 13	Yellow 8	Red 5	Green 8	Yellow 12	Red 2	Green 6	Yellow	Red 2	Green 23	Yellow 16	Red 9

constituted morbidity, however, practically all such cases had the minimum requirement of temperature elevation.

The first general grouping of cases were as to the gravida and gravida-para combinations. There were 166 primagravida women and 334 multipara. Approximately 33½ per cent of the 500 inductees were primagravida. There were 61 green cases, 37 yellow cases, and 68 red cases of this primagravida grouping. At a glance this shows the danger of inducing a woman with her first pregnancy, 41 per cent morbidity.

When the age incidence was brought into the picture there was a definite higher morbidity in the younger women, in the teen age to 20-year group, and in the 20 to 25 years of age group. Further observation divided the cases into six general groups of classification as follows:

1. Toxemias	47 cases	21 Red	44% Morbidity	9% Incidence
2. Disproportion	31 cases	19 Red	60% Morbidity	6% Incidence
3. Ruptured membranes (not followed by induction of labor within 12 hours)	14 cases	11 Red	80% Morbidity	3% Incidence
4. Post mature as to estimated date of confinement	109 cases	27 Red	25% Morbidity	20% Incidence
5. Ante estimated date of confinement	168 cases	31 Red	18% Morbidity	33% Incidence
6. Estimated date of confinement	131 cases	19 Red	14% Morbidity	26% Incidence
Total	500 cases	128 Red	25% Morbidity	99% Incidence

Taking the first group of toxemias, it was noted that in 1925 to 1927 there were 130 cases classified as toxemias which were not induced, and 20 cases which were induced, which means that only 13 per cent of the toxemias of thirty-six weeks' gestation or more required induction in their management. Practically all observers have noted the ease with which toxemias of pregnancy are usually induced by medical means. The other groups, 1928 to 1934, and 1943 to 1944, showed 14 per cent and 10 per cent, respectively, that required induction. It has been suggested that the toxemia produces infarction in the placenta which has the tendency to terminate pregnancy. However, all observers list toxemias as a cause for induction of labor, if and when management of the cases calls for termination of pregnancy. There is no uniform agreement in the literature on management of the other five general groupings.

with one maternal death occurred in addition. Fortunately, spontaneous rupture of the membrane is usually followed by labor or it is possible to induce labor without too much difficulty.

DePuy,<sup>13</sup> from a study of failure in induction of labor, concluded that in elective induction, when labor fails to follow rupture of the membranes and attempts to stimulate pains with oxytocics fail, the patient should be put to bed and let alone since there may be an interval of from two to four days before labor starts. It is pointed out that the complications listed by DePuy<sup>13</sup> which follow rupture of the membranes for the induction of labor are in cases where the cervix is not prepared for the advent of labor. This should serve as a warning that if the membranes are ruptured electively for the induction of labor the patient must be at the threshold of labor, or a high morbidity incidence will occur. Plass<sup>8</sup> showed, in comparing spontaneous rupture of the membranes with elective rupture of the membranes, that labors of more than thirty hours duration were two and one-half times as common in the elective rupture figures than in the spontaneous rupture of the membranes. However, the great majority of his spontaneous ruptures were in cases that were in active labor. Morton and Adair<sup>14</sup> concluded from a clinical study of premature rupture of the membranes in which there were 536 primiparas and 464 multiparas, that infant mortality is higher if delivery occurs after a latent period of fifty-five hours or more. Seventy-one cases had artificial rupture of the membranes. One hundred eighty-two cases required castor oil, quinine, pituitrin, or the use of a bag in combination. Of 63 patients who were febrile, 41 had some type of operative procedure. Eighty patients with membranes ruptured over 24 hours, not operated upon, gave 6.4 per cent morbidity. The total morbidity for the 1,000 cases was 6.3 per cent. The general hospital morbidity rate was 7.7 per cent. These findings might tend to obscure the real danger found in the rarer conditions of failure to induce labor as recorded in the 14 cases in this series of 500 cases studied. It will be noted that in the 1943 to 1944 series, there were no cases of spontaneous rupture of the membranes not followed by active induced labor within a 12-hour period. This shows a better selection of cases of those nearer the time labor would have started spontaneously.

In addition to the morbidity of 80 per cent as shown in Table IV, there was a maternal mortality of 21 per cent and a fetal mortality of 20 per cent. Ninety per cent of the cases acquired cervical laceration in the morbid group, and 50 per cent in the nonmorbid group. The hours of labor averaged twenty-five hours for the morbid and twenty hours for the nonmorbid group. Birth weights of the babies in the nonmorbid group were 800 Gm. higher than of those in the morbid group.

Caution should be exercised in selecting cases for induction by using this method of rupturing the membranes, since failure of labor to start leads to a prohibitive morbidity. However, when a mistake is made, the use of sulfonamides and penicillin prophylactically instead of forcing labor by oxytocics and mechanical means might give a lower morbidity rate. Intrauterine fetal infection, especially lung infection of colon bacilli etiology, was noted in this group.

The fourth general grouping "postmature as to estimated date of confinement, three days to twenty-one days plus," showed that 109 cases out of the 500 studied gave a 25 per cent morbidity, this figure was rather surprising, as one could logically reason that such patients should be prepared for labor and that induction should produce less unfavorable results. However, uterine dystocia was present in about 10 per cent of the cases. On the whole, the birth weights were above the average. Rathbun<sup>15</sup> showed that from a study of 250 cases of postmaturity, the period of postmaturity was longer on the average for stillborn infants 24.4 days beyond term, as against 19.6 days for



of choice. Fetal mortality and morbidity and the high incidence of puerperal infection have been shown by Douglas and Stander<sup>11</sup> to occur with prolonged labors. The difficulty of inducing labor in this group is in contrast to the toxemia group. Stander<sup>11</sup> has also pointed out that the morbidity and mortality have been decreased when long labors have been allowed to terminate spontaneously without operative interference. When disproportion is the problem, such a happy termination cannot be counted upon. Connen and Jones<sup>12</sup> showed that 20 per cent of interference had been unnecessary as the size of the children had been overestimated, or that subsequent labor resulted in spontaneous delivery of babies definitely larger than those born following induction. This was true in five cases of this series. It seems therefore, that induction of premature labor, in the management of a contracted pelvis, should not be considered a justifiable procedure. However, termination of pregnancy after the child has attained full maturity, with an attempt at medical induction and if failure occurs, a repetition within a few days might be justified, but cannot be recommended as a procedure of choice. If the membranes are ruptured, one must be prepared to do a low cervical cesarean operation within twenty-four to thirty-six hours after rupture of the membranes if labor is not successful.

Birth weights of babies here were the same average for morbid and non-morbid cases. The hours of labor were almost four times as long in the morbid cases as in the nonmorbid group, with an average of nine hours. Eighty per cent of the morbid and 40 per cent of the nonmorbid cases acquired cervical laceration. A high maternal and fetal morbidity and mortality condemn induction of labor unless it is instituted very near to the onset of spontaneous labor, which was not the picture in this grouping of disproportion between fetus and pelvis.

The third general grouping "spontaneous rupture of the membranes not followed by active induced labor within 12 hours," fortunately consisted of only 14 cases out of the 500 studied, but the high morbidity of 80 per cent stresses the danger in such a situation. There were two patients with placenta previa and one marginal placenta in this group. This of course increased the morbidity, however, a prolapsed cord, Bandl contraction ring of the uterus, intracranial injury, a case of Dührssen's incision of the cervix, and two cesarean sections

TABLE IV. GROUP 3; SPONTANEOUS RUPTURE OF THE MEMBRANES NOT PRODUCTIVE OF LABOR WITHIN 12 HOURS  
(Which were 3% of the 500 cases studied)

1. Method of induction	Oxytocic	85%
	Mechanical induction	43%
	Cesarean sections	15%
2. Average hours of labor and birth weights	Morbidity cases averaged	25 hours and 3,000 Gm.
	Nonmorbidity cases averaged	20 hours and 3,800 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence	90%
	Nonmorbidity cases incidence	50%
4. Morbidity 80% maternal and fetal combined	50% Gravida—i	Maternal morbidity 58%
	30% Multipara	Maternal mortality 21%
		Fetal morbidity 22%
		Fetal mortality 20%
5. Latent sequelae	No lesion	14%
	Lesion	86%

Subsequent record on 64% of cases.

No subsequent record on 36% of cases.

*Diagnosis and Procedures:* Placenta previa; postpartum hemorrhage; terminal ruptured uteri; separation of symphysis; retrodisplacement of uteri; cervicitis with laceration; parametritis; ligation of uterine arteries; cervical branches; cauterization of cervix, uteri, for laceration; pessary for retrodisplacement.

TABLE VI. GROUP 5; INDUCED MORE THAN TWO DAYS BEFORE THE ESTIMATED DATE OF CONFINEMENT  
(36 weeks 2%) (37 weeks 25%) (38 weeks 65%) (39 weeks 8%)  
(Which were 33% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic	95%
	Mechanical induction } Bags	14%
		2%
	Cesarean sections	0%
2. Average hours of labor and birth weights	Morbidity cases averaged	14 hours and 3,200 Gm.
	Nonmorbidity cases averaged	10 hours and 3,500 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence	70%
	Nonmorbidity cases incidence	25%
4. Morbidity 18% maternal and fetal combined	10% Gravida—i	Maternal morbidity 11%
	8% Multipara	Maternal mortality 0%
		Fetal morbidity 7%
		Fetal mortality 4%
5. Latent sequelae	No lesion	40%
	Lesion	60%

Subsequent record on 43% of cases.

No subsequent record on 57% of cases.

*Diagnosis and Procedures:* Phlebitis; parametritis; cervical laceration; prolapse of uterus; retrodisplacement of uterus; hysterectomy complete; abdominal for uterine suspension; operation for cystocele and rectocele; Manchester operation; perineorrhaphy; cauterization of cervix; conization of cervix.

TABLE VII. GROUP 6; ELECTIVE INDUCTION AT ESTIMATED DATE OF CONFINEMENT—PLUS OR MINUS TWO DAYS  
(Which were 26% of the 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic	98%
	Mechanical induction } Bags	4%
		0%
	Cesarean sections	2%
2. Average hours of labor and birth weights	Morbidity cases averaged	20 hours and 3,300 Gm.
	Nonmorbidity cases averaged	8 hours and 3,400 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence	70%
	Nonmorbidity cases incidence	20%
4. Morbidity 14% maternal and fetal combined	8% Gravida—i	Maternal morbidity 10%
	6% Multipara	Maternal mortality 2%
		Fetal morbidity 4%
		Fetal mortality 2%
5. Latent sequelae	No lesion	40%
	Lesion	60%

Subsequent record on 35% of cases.

No subsequent record on 65% of cases.

*Diagnosis and procedures:* Phlebitis; parametritis; retrodisplacement; myoma of uterus; cervicitis with laceration; prolapse of uterus; vaginal plastic operation for cystocele and rectocele; cystitis; hysterectomy complete; abdominal for suspension of uterus; cauterization and conization of cervix.

former group, failure to induce was taken more seriously and mechanical means were resorted to, giving a higher incidence of cervical laceration and much longer labors, whereas with this group, failure to induce was not taken seriously and another attempt was made nearer to the threshold of spontaneous labor.

The last general classification was "elective induction at estimated date of confinement, plus or minus two days." There were 131 such cases, an incidence of 26 per cent, giving a morbidity rate of 14 per cent. This is the lowest morbidity rate of the six general classified groups, and it is quite logical that elective induction at the estimated date of confinement, excluding toxemias, disproportion, and spontaneous rupture of membranes which failed to induce within a twelve-hour period, would yield the lowest morbidity.

TABLE V. GROUP 4, POSTMATURITY AS TO ESTIMATED DATE OF CONFINEMENT  
(3 days to 21 days plus)  
(Which were 22% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		97%
	Mechanical induction	Bags	14%
		Bougies	2%
	Cesarean sections		3%
2. Average hours of labor and birth weights	Morbidity cases averaged		26 hours and 3,600 Gm.
	Nonmorbidity cases averaged		13 hours and 3,600 Gm.
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		55%
	Nonmorbidity cases incidence		20%
4. Morbidity 25% maternal and fetal combined	11% Gravida—i	Maternal morbidity	16%
		Maternal mortality	0%
	14% Multipara	Fetal morbidity	9%
		Fetal mortality	4%
5. Latent sequelae	No lesions		40%
	Lesions		60%

Subsequent record on 44% of cases.

No subsequent record on 56% of cases.

*Diagnosis and Procedures:* Separation of symphysis; parametritis; cervical laceration; retrodisplacement of uterus; hysterectomy complete; abdominal for retrodisplacement of uterus; suspension; cauterization and conization of cervix; pessary.

live babies. He concludes there is no more need for fear that the fetus will be lost in utero without cause than exists at term. Postmaturity occurred 1 in 13.2 deliveries in his series. It would be an assumption that, because labor does not start within two or more weeks after the estimated date of confinement, that the baby is postmature. Cornell<sup>10</sup> states that patients thirty-five days over the estimated date of confinement have been known to give birth to babies weighing 3,300 Gm. to 4,200 Gm. showing a wide variation in fetal size. There is an equally wide variation in the series of cases here presented, as to fetal weights. One case of a 4,600 Gm. child was induced by means of ruptured membranes, resulting in a ten-hour labor, without birth injury or injury to the cervix, as compared with another case of a 3,100 Gm. child induced by means of ruptured membranes and infundin, producing a ten-hour labor, resulting in intracranial birth injury and a lacerated cervix. Postmaturity as to estimated date of confinement is not a reliable diagnosis. It is extremely difficult to correlate the fetal size with the calculated date of confinement.

The fifth general classification "induced more than two days before the estimated date of confinement," thirty-six to thirty-nine weeks inclusive, was tabulated as follows: thirty-six weeks, 2 per cent incidence; thirty-seven weeks, 25 per cent incidence; thirty-eight weeks, 65 per cent incidence; thirty-nine weeks, 8 per cent incidence. There were 168 such cases out of the 500 cases studied and there was a morbidity of 18 per cent. It was noted that morbid cases had average lower birth weights than the nonmorbid cases studied in this grouping. This was taken to mean, together with the slightly longer hours of labor, that these patients were not at the threshold of labor. Please bear in mind that these cases were electively induced without indications of toxemia, or disproportion, or spontaneous rupture of the membranes. Ninety per cent were between thirty-seven and thirty-nine weeks of gestation and were for the most part convenient inductions. Most of the morbidity was due to intracranial injury and prolapsed cord. Cases that were not pushed, but were allowed to be failures of induction in which spontaneous labor later occurred in the second or third attempt at induction some four to five or ten days to two weeks later, usually resulted in no morbidity unless the membranes had been ruptured. It is thought that the lower morbidity rate in this series, as compared with the morbidity rate of the preceding group, namely, postmature as to date of confinement, could be explained as follows: in the

difficult to evaluate the condition of the cervix after spontaneous and elective rupture, because of "out-of-city" patients; however, the experience gained from routine speculum examinations when patients were discharged from the hospital eight to ten days after delivery confirmed the observations of Schumann<sup>19</sup> that dry labor does not increase the incidence or degree of cervical injury.

The question of cervical laceration and injury to the cervix has been of particular interest and study for the past sixteen years, and was one of the factors in arousing interest in this study of morbidity associated with the induction of labor. It seems that the only reliable clinical means available at the present time as to whether a patient is crossing the threshold of labor is the condition of her cervix. One year ago a patient entered the St. Louis Maternity Hospital with a full-term abdominal pregnancy. Those in charge of the case reported the patient to be in labor, the cervix to be soft, effaced, and dilated, although there was no presenting part within the uterus and there was no uterine bleeding. This condition of the cervix has been noted and was referred to by Cornell and Lash.<sup>20</sup> The theory of the onset of labor as having a hormonal etiology which causes softening, thinning, and dilatation is borne out by clinical observations. It would therefore be expected that, if labor were induced when such changes were present, labor would proceed normally without laceration or injury to the cervix, not because of the method of inductions used, but because of the prepared condition of the lower uterine segment and cervix.

Hamilton,<sup>21</sup> in his article on "Preliminary Stage of Labor," points out that when labor seems to be in process without the above noted changes in the cervix and when intervention occurs during this period, morbidity results. Unnecessary cesarean sections for cervical dystocia are done during this period, whereas if the patient were given sedation, normal labor would occur at a later date.

Calkins,<sup>22</sup> in his article, "Predicting Length of Labor; First Stage," states that it is interesting to consider the etiology in variation in the cervix and in uterine contractions. The cause is not anatomic. It is almost certainly physiologic. The etiology of the onset of labor is inextricably involved in both cervical consistency and effacement, and uterine contractions. Only when this physiologic factor has been found can the least favorable patients be prepared to enter labor with unresisting cervix and good uterine contractions.

With these points in mind, it is readily seen that patients induced by Holman,<sup>9</sup> Plass,<sup>8</sup> Gillett,<sup>17</sup> and others<sup>4</sup> referred to are a literally hand-picked selected group and that no increase in morbidity should be expected unless there is an error in judgment as to the case selected for induction not being ready for impending labor.

During the past three years no ward patients at the St. Louis Maternity Hospital have been induced except for toxemia. All ward patients are followed in the Clinic and referred to the Cervicitis Clinic if cervical laceration or lesions are found. With the elimination of pituitary injections, the incidence of cervical lacerations has been reduced an estimated 75 per cent.

Severe cervical lacerations occurring with an induced labor constituted a morbidity factor in these 500 cases of induced labor reported. In multiparas with cervical laceration and no history of previous induction of labor, laceration was not recorded as morbidity unless definite evidence of new deep laceration was reported with the induced labor.

The subgrouping of only morbid cases into acute endometritis, hemorrhage, and transfusion incidence gives the picture shown in Table VIII.

The incidence of acute endometritis and hemorrhage is almost the same except in the contracted pelvis, pelvic disproportion (B) Group. Here the

It is to be expected, as pointed out in 1944 by Gillett<sup>17</sup> reporting 1,000 cases of elective induction by rupture of the membranes, that the optimum time for elective induction was as close to term as possible. He used the following points in determining the time for elective induction: first, calculated date of confinement; second, fundal measurements; third, the ripeness of the cervix; the latter being the most important. Nonengagement of the fetal head was considered an absolute contraindication to artificial rupture of the membranes, because of the increased risk of the cord prolapsing. He claims that a well-effaced cervix which was thin and soft was a reliable indication of impending labor in both primiparas and multiparas. In the multiparas these cervical changes were not always present before the onset of labor. One hundred per cent induction occurred within a twelve-hour period. He states that the average latent period, from the time of rupturing the membranes to the onset of labor, was approximately one hour for all cases. The average duration of labor in the primiparas was six hours, and three hours for the multiparas. An oxytocic agent (pitocin) was used in his series in order that the procedure of induction occur in all cases.

The maternal mortality in his series was zero, the puerperal morbidity was 5.1 per cent, no stillbirth occurred, and he explains this fact by limiting induction to normal patients only. Fetal distress, prior to induction, was another contraindication to inductions. Neonatal mortality was 0.8 per cent. Four cases had pneumonia, congenital anomalies occurred in two cases, hemorrhagic disease in the newborn in one case, and an undetermined cause of death in another. He concludes that the best technique for inducing labor is a hot soapsuds enema, hypodermic pitocin, and low rupture of the membranes. There were 642 multiparas and 358 primiparas, totaling 1,000 patients reported in Gillett's series.

Holman<sup>18</sup> states in a personal communication, that he has had a combined experience of over 2,000 cases of induction of labor with statistics on morbidity and infantile mortality practically identical with those published in 1937. There were no maternal deaths, and a maternal morbidity of 5.3 per cent. Fetal mortality, uncorrected, was 3.5 per cent. He used pituitary extract and after one or two doses, routinely ruptured the membranes. Pentobarbital is used to keep the patient tranquil and free from pain.

Plass<sup>8</sup> reports 1,000 consecutive normal parturient women with cephalic presentations, in which spontaneous rupture of the membranes occurred, called Group 1, and compared them with 1,000 normal women in whom labor was induced by elective rupture of the membranes, called Group 2. Twenty-five per cent of the patients in each group had postpartum temperature elevation of 100.4° F. or above. The incidence of true puerperal morbidity, as indicated by the presence of fever for more than one day, was slightly higher in Group 2, the induced series, and may be explained by the inevitable vaginal manipulation.

There were, however, no serious infections, and persistent fevers were recorded in each group to about the same extent. He states that labors induced by artificial rupture of the membrane do not differ materially from those which start spontaneously. Intrapartum infections were twice as frequent in the induced series, and this increase may be attributed to the procedure. The duration of the labor showed that there was a definite increase in the number of "thirty hour or more labors" among the women in the Group 2 induced series. In each division of the multigravidas, the percentages of longer labors were higher in the induced group than in Group 1. He states that the birth process tends to be either slightly shortened or somewhat prolonged when labor is induced electively by premature rupture of the membranes, but gives no clue as to the factors producing either tendency. Plass<sup>8</sup> states that it was

elective induction be considered without undue assumption of risk. Evasion of these requirements has given rise to hazards ranging from prolongation of the 'latent period,' difficulties with resistant cervixes, emergency cesareans, and intrapartum infections to stillbirths and maternal death."

It has been established that there is morbidity associated with the induction of labor under certain conditions. The results of a study of those cases which failed to induce, 13 per cent of the 500 cases presented, are shown in Table IX.

TABLE IX. FAILURE TO INDUCE (2 TO 14 DAYS PLUS)  
OF ALL INDUCED—13% OF 500 CASES

Of all attempts to induce contracted pelvis (pelvic disproportion)	35% failed
Of all attempts to induce toxemia patients	25% failed
Of all attempts to induce ruptured membranes not productive of labor within 12 hours	21% failed
Of all attempts to induce the antemature more than two days before the estimated date of confinement	11% failed
Of all attempts to induce the postmature as of the estimated date of confinement	9% failed
Of all attempts to induce $\pm$ two days of the estimated date of confinement	9% failed

The groups contracted pelvis-pelvic disproportion; toxemia; ruptured membranes not productive of induced labor within 12 hours; and antemature, more than two days before the estimated date of confinement, show from 35 per cent to 11 per cent of all such cases failed to induce, while 9 per cent of the postmature and 9 per cent of the plus or minus two days of the estimated date of confinement failed to induce. The greatest failure to induce occurred in cases which were the furthest removed from the natural onset of spontaneous labor.

Now, if the 67 cases out of the 500 cases which failed to induce are totaled as to incidence, the antemature more than two days before the estimated date of confinement show that 28 per cent failed to induce. Next were the toxemia cases and those of two days plus or minus of the estimated date of confinement. Then the contracted pelvis-pelvic disproportion with 16 per cent incidence of failure to induce. Next came the postmature as of the estimated date of confinement, with 15 per cent incidence; and last, 4 per cent incidence of failure for the ruptured membrane group. With the exception of ruptured membranes, the lowest, and antematurity the highest of failure to induce, the other groups varied by 3 per cent, two of the groups were the same per cent, and the other two groups varied by 1 per cent. Again there is strong evidence of some basic factor underlying the cause for the onset of labor in each case.

Now if the incidence of failure to induce is broken up into two days, four days, seven days, and fourteen days of failure, the percentages are 34, 27, 20, and 18. Only the ruptured membranes not followed by induced labor within twelve hours showed no failure to induce past a two-day period. However, the morbidity of this group was 80 per cent. The highest percentage of failure occurred within the two-day and four-day groups, but the incidence of seven-day and fourteen-day failure varies only from 1 to 2 per cent. All this would indicate some basic factor in failure to induce any given case.

For comparison 500 cases of natural spontaneous labor were studied as to the time labor started in reference to the estimated date of confinement. These were 250 ward cases at the St. Louis Maternity Hospital and 250 private patients at the same hospital.

As to the onset of spontaneous labor, 27.7 per cent were from minus one to minus ten days before the estimated date of confinement; 6.9 per cent were

greatest concerted effort was made to force labor and delivery, and most of these cases were before the common practice of blood transfusions. Manipulation which introduces infection, and blood loss which lowers the resistance to infection brings about morbidity. Failure to keep the uterus well contracted contributes to both infection and blood loss. In no group did the incidence of hemorrhage exceed the incidence of acute endometritis by more than 1 per cent.

TABLE VIII. MATERNAL MORBIDITY; MORBIDITY CASES ONLY

CLASSIFICATION GROUPS	ACUTE ENDOMETRITIS 15% INCIDENCE	HEMORRHAGE 12% INCIDENCE	TRANSFUSION 33% INCIDENCE*
A Toxemia	21% of all A cases	17% of all A cases	37%* of all A cases
B Contracted pelvis, pelvic disproportion	26% of all B cases	10% of all B cases	0%* of all B cases
C Ruptured membranes, not productive of labor within 12 hours	30% of all C cases	30% of all C cases	75%* of all C cases
D Postmature as of the estimated date of confinement	4% of all D cases	5% of all D cases	16%* of all D cases
E Antemature—more than 2 days before estimated date of confinement	5% of all E cases	5% of all E cases	50%* of all E cases
F ± 2 days of the estimated date of confinement	5% of all F cases	5% of all F cases	14%* of all F cases

\*Percentage of hemorrhage cases requiring transfusion.

In the toxemia and contracted pelvis groups the incidence of infection was greater than the hemorrhage incidence. In ruptured membranes not followed by induced labor within twelve hours, the highest incidence of acute endometritis and hemorrhage was found and the percentage was identical. Douglas and Davis<sup>23</sup> state that: "If labor continues sufficiently long with ruptured membranes, clinical signs of infection will always occur, even in the absence of pelvic examinations or other possible outside sources of infection. The development of intrapartum infections does not imply that the postpartum course will be febrile, or the patient classified as having morbidity by any of the standards commonly employed. If following premature rupture of the membranes no labor whatever develops, and the patient is kept at rest in bed, then infection is unlikely to occur." They also point out that infections may be decreased by control and restoration of blood loss. Sulfadiazine and/or penicillin given early may be efficacious, while late in the course of the disease they are less effective.

Royston<sup>24</sup> states, "The widespread, injudicious use of pituitary injections during labor has undoubtedly increased maternal morbidity (from tears), and fetal morbidity (from intracranial injuries)."

Thompson<sup>25</sup> states, "There are and can be no indications for elective induction of labor. The method proposed by Slemmons<sup>6</sup> has many meritorious features. The requirements are logical; the technique is simple; the results are usually most gratifying. However, contraindications exist unless (1) term has been reached, (2) the head is engaged, (3) the cervix is effaced, and (4) dilatation has begun. When one has questioned himself closely and has satisfied himself that these requirements have been met, then, and only then, may



TABLE XII. AN ANALYSIS OF 500 CASES: 250 WARD, 250 PRIVATE, WHOSE LABORS WERE SPONTANEOUS, NOT INDUCED

ESTIMATED DATE OF CONFINEMENT	BIRTH WEIGHTS	HOURS OF LABOR
-25 Days 4.6%	(2,350-3,880 Grams) Average 3,090	(3-60 Hours) Average 14
-21 Days		
-20 Days 5.0%	(2,790-4,350 Grams) Average 3,260	(3-60 Hours) Average 14
-16 Days		
-15 Days 7.0%	(2,700-3,950 Grams) Average 3,110	(2-25 Hours) Average 10
-11 Days		
-10 Days 13.4%	(1,700-3,900 Grams) Average 3,260	(2-32 Hours) Average 11
- 6 Days		
- 5 Days 14.3%	(2,940-4,110 Grams) Average 3,400	(3-26 Hours) Average 10
- 1 Day		
E.D.C. 6.9%	(2,950-4,330 Grams) Average 3,580	(2-21 Hours) Average 9
+ 1 Day 19.4%	(2,750-4,410 Grams) Average 3,480	(2-24 Hours) Average 9
+ 5 Days		
+ 6 Days 17.6%	(3,031-4,100 Grams) Average 3,470	(2-31 Hours) Average 10
+10 Days		
+11 Days 3.7%	(3,170-3,690 Grams) Average 3,430	(4-19 Hours) Average 11
+15 Days		
+16 Days 3.7%	(3,425-4,290 Grams) Average 3,680	(5-22 Hours) Average 12
+20 Days		
+21 Days 4.6%	(3,010-3,800 Grams) Average 3,460	(3-20 Hours) Average 8
+25 Days		

27.7% minus 1 to minus 10 days before estimated date of confinement.

37.0% plus 1 to plus 10 days after estimated date of confinement.

6.9% on the estimated date of confinement.

Total of 71.6% within a plus or minus 10 days of the estimated date of confinement.

greater birth weights were seen in all cases which did not have morbidity associated with the induction of labor. This was taken to mean that those cases which showed no morbidity were at the threshold of spontaneous labor when labor was induced.

There has been no attempt to compare the induced 500 cases with the above 500 control cases except as to birth weights and hours of labor. The calculated morbidity of the spontaneous labor group was about 10.5 per cent combined maternal and fetal, as against 25 per cent combined maternal and fetal for the induced labor group. It is felt that more information is obtained as to causative factor in morbidity if different groups of induced labors are studied. For example, the highest morbidity of any group of the induced cases was 80 per cent for the ruptured membranes not followed by induced labor within twelve hours; and the lowest morbidity of 14 per cent occurred in cases induced at estimated date of confinement. When membranes were ruptured in this group the cervix was effaced and dilatation had begun; the head was well fixed or engaged within the pelvis and induced labors proceeded as normal spontaneous labor because these patients were already in early labor when inductions were begun.



TABLE X. THOSE 67 CASES WHO FAILED TO INDUCE

28%	Incidence were—antemature—more than 2 days before estimated date of confinement (the least concerted efforts were made here)
18%	Incidence were—toxemia
18%	Incidence were— $\pm$ 2 days of the estimated date of confinement
16%	Incidence were—contracted pelvis, pelvic disproportion (the greatest concerted efforts were made here)
15%	Incidence were—postmature as of the estimated date of confinement
4%	Incidence were—ruptured membranes not productive of labor within 12 hours
99%	Total

TABLE XI. INCIDENCE OF FAILURE TO INDUCE

	2 DAYS FAILURE	4 DAYS FAILURE	7 DAYS FAILURE	14 DAYS FAILURE
Toxemia	5%	5%	4%	4%
Contracted pelvis, pelvic disproportion	3%	6%	3%	4%
Ruptured membranes not productive of labor within 12 hours	4%	0%	0%	0%
Postmature as of the estimated date of confinement	6%	3%	4%	2%
Antemature—more than 2 days before estimated date of confinement	13%	4%	6%	4%
$\pm$ 2 days of the estimated date of confinement	3%	9%	3%	4%
Total 99%	34%	27%	20%	18%

on the estimated date of confinement; 37 per cent were from plus one to plus ten days after the estimated date of confinement. Therefore, from ten days before to ten days after the estimated date of confinement, a total of 71.6 per cent of labor occurred.

At the estimated date of confinement the average birth weight was 3,580 grams. This birth weight was not surpassed until the average of 3,680 Gm. (only 100 grams more) was attained by the plus sixteen to plus twenty days after the estimated date of confinement group. The average of the plus one day to the plus fifteen days after the estimated date of confinement was less than the average weight of those babies born on the estimated date of confinement. Now the weights of the plus twenty-one days to plus twenty-five days were less than the birth weights of the estimated date of confinement group. This would probably indicate a mistake in calculation of the expected onset of labor.

All of those born before the estimated date of confinement averaged less than the estimated date of confinement group or plus days group following the calculated date, but many individual birth weights were 3,910 to 4,300 Gm. It is clearly shown that the calculated date of confinement proposed by Naegele is of little value in fixing the date for the onset of labor or determining the size of the newborn.

Now when the hours of labor are tabulated it is interesting to note that the averages vary from fourteen hours for the most immature to eight hours for the most postmature. Nine hours was the average for those labors which occurred at the estimated date of confinement and those which were plus one to plus five days after the calculated date. However, the group which had the highest birth weights, plus sixteen days to plus twenty days past the estimated date of confinement, did have an average of twelve hours for the labors. The longest labor in this group was twenty-two hours as against sixty hours for the two most immature groups. These shorter hours of labor with the

2. The increase in morbidity is caused by forcing labor before the cervix, lower uterine segment, and uterus have been prepared for labor.

3. The character and results of induced labor approach that of natural spontaneous labor only when the induced labor precedes by forty-eight hours or less the time when spontaneous labor would have occurred anyway.

4. This means that induction of labor has *obstetric* usage mainly in the management of the toxemia patient, including the diabetic.

5. For the management of contracted pelvis, pelvic disproportion, induction has little or no usage.

6. For the management of postmaturity, induction has little or no usage.

7. Induction of labor after spontaneous rupture of the membranes may be a dangerous procedure.

8. The morbidity incurred by induction of labor must be evaluated against any questionable advantages in such management.

9. Elective induction of labor, which would have occurred in twenty-four hours to forty-eight hours later, gives little or no morbidity.

10. Such elective induction is of little or no obstetrical advantage, but rather has convenience and order as its justification.

I desire to express my appreciation to Miss Bessie E. Taylor, Chief Historian in charge of record room at Barnes and St. Louis Maternity Hospitals, who made available the histories and data for statistical study, and to Dr. Seymour Monat, Resident at St. Louis Maternity Hospital, who tabulated the data on 150 cases of the 1944 series.

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## Discussion

The contention seems trite that only such patients that are entering the threshold of labor can be induced without morbidity caused by the induction, yet this is the plain conclusion from this study. The work of Lyon<sup>3</sup> referred to in the introduction would bear out this conclusion.

By courtesy of Dr. Willard Allen, a patient in his department whose pregnandiol excretion in the urine was being studied failed to induce with infundine injections until repeated attempts to induce with pituitary extract some forty-eight to seventy-two hours later were shown to have coincided with the fall in pregnandiol, at which time labor started and concluded successfully.

Unfortunately, the time consumed and expense involved make it for the present, at least, impossible to use pregnandiol excretion as a means of determining when labor will start. It may be asked if other oxytocics such as quinine, ergonovine, and methergen have any unique ability to induce labor.

Murphy<sup>26</sup> has shown with his study of uterine contractions with the Lorand tocograph the pattern of false labor and its relation to premature labor, that false labor may be followed by premature labor.

Lyon<sup>3</sup> shows a case of irritable uterus and placenta bleeding with a drop from NaPG of 70 mg. to 30 mg., from April 27 to April 30. A rise to 70 mg. again on May 3, and premature delivery May 14, after a fall to 10 mg. on May 12. It will be recalled that charts designed to show reason for failure to induce would indicate the frequency of forty-eight-hour intervals from the first attempt to a successful attempt at induction.

Marchetti, Kuder, and Fitch<sup>27</sup> selected 500 cases for study of the effect of antepartum administration of small doses of quinine. Labor was not shortened, and with primiparas it was lengthened. The percentage of patients who delivered before the expected day of delivery was slightly higher than in a control series. Adair and Davis<sup>28</sup> report that ergotocin gave inconclusive results for the induction of labor. Farber<sup>29</sup> reports 43 consecutive cases of induced labor with five failures when the new drug methergen is used. This preparation, he states, is similar to ergonovine but contains an additional CH<sub>2</sub> group. Here again the same principles would seem to apply as to the ability to induce.

Eastman<sup>30</sup> outlines the requirements to be met for induction in the diabetic patient as follows: A sterile vaginal examination is made to determine, (1) if the head is at or below the spines; (2) if the cervix admits easily one or two fingers, and (3) if the cervical canal is less than 1 cm. long. The infant must be between 3,000 and 3,500 Gm. in weight. Then the membranes are stripped back and ruptured. If the cervix is not favorable for induction and there is no urgency, the patient is allowed to go to term or to such a time as the cervix is favorable. If urgent, a cesarean section is done. This would seem to be the procedure of choice for all toxemias and diabetics.

Bouton<sup>31</sup> does not favor prematurely induced labor for the erythroblastic fetus, as attention is called to the possibility of increasing damage by labor. Whether this represents an actual hazard in practice remains to be seen, but it must be considered in weighing the relative merits of labor induction versus cesarean section.

## Conclusions

1. It has been shown that there can be severe morbidity incurred with the induction of labor.

from the ideal method in managing such cases. I believe that a policy of noninterference with pregnancy, a test of labor at term, and cesarean section at the properly selected time is much the better plan of management.

His statistics, revealing the high incidence of morbidity and mortality associated with induction of labor among cases in which the membranes had been ruptured twelve or more hours, are worthy of careful study. A combined maternal and fetal morbidity of 80 per cent along with a maternal and fetal mortality of 21 and 20 per cent, respectively, is indicative of the seriousness of the problem this type of case presents. Note that 15 per cent of these cases were delivered by cesarean section. I feel that cases presenting definite evidence of rupture of the membranes should not be left awaiting spontaneous onset of labor for an indefinite period of time. It is our policy to attempt to initiate labor in such cases within six to twelve hours following spontaneous rupture by medical induction. The administration of castor oil followed, if necessary, by pituitary extract intranasally or, if not effective, by minute doses hypodermically has given good results. It is important that such cases be spared surgical induction and that operative interference be reduced to a minimum in their management.

DR. ALBERT W. HOLMAN, Portland, Ore.—In 1935, my associate, Dr. Mathieu, and I reviewed our statistics on 750 cases of induction of labor with a control series of 750 cases of noninduced labor. I feel that one must differentiate between the medicinal and the mechanical types of induction. The results are just as different as in automobile accidents and typhoid fever. This is the third paper I have heard presented before this Association where bags, bougies, and oxytocics are lumped together in discussions of inductions of labor. You cannot figure them that way. Those done medically are very different from those done mechanically.

In our 750 cases of induced labor we had a fetal mortality of 0.9 per cent. We had no cases that did not go into labor. It makes a lot of difference whether the induction of labor is done by one trained person or whether left to the nurses in the delivery room, where perhaps one nurse will start an oxytocic, and after several injections another nurse will take over. I am making a plea for subsequent studies of induction of labor to differentiate between the medical induction and the mechanical induction of labor.

DR. M. PIERCE RUCKER, Richmond, Va.—I have induced labor by rupture of the membranes over 4,000 times. The record is shown in the table.

Unfortunately, there are included consultation cases. If I had not included those the two groups would have been more comparable. For instance, four of the six maternal deaths were in consultation cases, but more particularly there would have been a better distribution of the severe complications of pregnancy. I was surprised, for instance, to find that in placenta previa there were more cases in the uninduced group than in the amniotomy group. The cases for amniotomy were not selected unless there were complications present. In a normal case the patient herself elected whether she wanted the day set at or near term. In the complicated cases, however, I tried to do what I thought best. Had the consultation cases been eliminated, I feel that there would have been a higher percentage of placenta previas in the amniotomy group.

There were 4,045 amniotomy cases and 2,138 others. The neonatal deaths were 1.1 per cent in the amniotomy cases and 4.2 per cent in all others. Stillbirths were 1.1 per cent in amniotomy cases and 5 per cent in all others. There have been some unfavorable selection in the "all others" cases. There were more eclampsias and ablatio placentae, etc. in the "all others." There were four detached retinas, three in the amniotomy cases and only one in all others. What I wanted to point out was that the morbidity was not increased by amniotomy. There were only 160 cases with afebrile puerperium, or 3.9 per cent, in the amniotomy cases and 155, or 7.2 per cent, in the others.

The surprising thing was the prolapsed cord cases. There were only eight in the 4,045 amniotomy cases in comparison with 21 in the other cases.

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### Discussion

DR. EMMETT D. COLVIN, Atlanta, Ga.—It is interesting to note that 48 per cent of the inductions were for the termination of pregnancy, either "electively," in 26 per cent, or, because of postmaturity, in 22 per cent.

While this and other investigations indicate fairly satisfactory results following the elective induction of labor presumably at or near term, the procedure is sufficiently radical to warrant a thorough discussion of the subject.

The results of my experience with induction of labor are similar to the conclusions drawn by Dr. Roblee.

In recent years, there has been a strong tendency to broaden the indications for termination of pregnancy at or near term by elective induction of labor, usually by artificial rupture of the membranes alone or in combination with oxytocics. For example, in our University Hospital, the incidence of induction increased from 1 in 23 to 1 in 6 labors during the past four years. Among the attendants it was found that the incidence of induction for diplomates and nondiplomate specialists in obstetrics had not increased, but the per cent of inductions had precipitously increased among general practitioners who became specialists during the war years as a result of suddenly inheriting a large volume of obstetric cases. The characteristic haste of such attendants to induce simultaneously a group of cases at or near term in order to save time and secure rest is shown by their frequent resort to cesarean section, and also by the readiness with which they perform difficult operative deliveries or injudiciously rely upon oxytocic drugs to terminate labor rapidly. The inevitable result of such a meddling policy is trauma. It is my belief that all cases admitted into hospitals for induction of labor should be studied by a governing board prior to induction.

I am not an advocate of elective induction of groups of women for convenience. We have met the problem of added volume and consequent loss of rest by the formation of an obstetric group in which the members rotate in shifts through the hospital and office hours. Under this plan outlined by Bartholomew in "Utopian Obstetrics" the members of the group secure ample rest and sleep. Thus, in our practice elective induction is limited, with exceptional cases, to multiparous women whose previous labors were rapid and those whose residence is a considerable distance from the hospital. To me, the latter type of patient is always a problem.

If pregnancy and labor are still to be regarded as a physiologic process, the burden of proof for a successful outcome following elective induction of labor becomes a moral and legal responsibility of those who so boldly interfere and accept responsibility for the management of unexpected complications after labor has been initiated in a normal process.

No one will argue against the wisdom of inducing labor in complicated cases of pregnancy where experience has taught that pelvic delivery offers the greatest degree of safety for the mother and fetus.

Dr. Roblee's figures reveal a high incidence of cervical damage among the induced cases. When labor is induced, the possibility of cervical trauma must always be kept in mind, not alone from a standpoint of danger at the time sustained, but also from that of its behavior during subsequent deliveries.

I have always doubted the wisdom of induction of premature labor in the management of a case of contracted pelvis. The potential dangers of a prolonged latent period, the unpredictable behavior of the uterine muscle, the unprepared cervix, and the immature fetus, in addition to the limitation of pelvic space, all combine to predict trouble from the start. Dr. Roblee's figures of a combined maternal and fetal morbidity of 60 per cent, along with a 3 per cent maternal and 23 per cent fetal mortality, offers proof that it is far

In regard to the use of pituitrin for induction of labor, I have definite fear. I seldom use it, and when I do it is only over a short period of time and in small doses. The principal objection is that pituitrin frequently initiates rhythmic contractions which may persist indefinitely, causing more than average discomfort for the patient, and resulting in no change in the condition of the cervix, as determined by vaginal examination. For some reason, contractions caused by pituitrin do not seem to have the effect of ordinary uterine contractions. I feel that pituitrin frequently complicates matters.

Something might be said about the selection of cases for induction. These days we do not hesitate quite as much to induce labor as we formerly did. We are almost inclined to feel as we do in regard to the use of outlet forceps, except that one must proceed with greater caution. In my opinion, an important factor in selection of cases is the estimated date of confinement. If, upon abdominal examination, pregnancy appears to be at term and the estimated date indicates that the patient is not due for three or four weeks, I would certainly not induce labor, for in such a case, if induced before term, one might be surprised to find that the fetus is below average weight and may not appear mature. For that reason, I have a high regard for the estimated date of confinement. Induction should always be around this date. Another factor of importance is the position and degree of engagement of the head. It is rather essential that the head be engaged even though the danger of prolapsed cord might be slight and that there be no malposition which may complicate the mechanism of labor. It is necessary, also, for the patient to be cooperative and willing. For reasons that are evident, one should not try to convince a patient, in any manner, that labor should be induced, nor is it wise to institute any unnecessary procedure in a patient who displays fear. When there is any doubt as to the maturity of the fetus or the position of the head, I resort to the use of the lateral roentgenogram. I have frequently stated that in most cases the head has a tendency to engage with the biparietal diameter in the true conjugate. In my opinion, the size of the biparietal diameter is the most reliable indicator of fetal maturity. If this measurement is 9.25 cm., I feel that the fetus is mature. The babies I have delivered through induction of labor are all mature. I would say that they might average a trifle smaller than the average of those in my noninduced series at term, but it is not my purpose to deliver as big a baby as possible. For the benefit of the mother, I think an average size baby is sufficient. Finally, I wish to state that the most important factor relative to rupture of membranes for the induction of labor is the condition of the cervix. If the cervix is elongated or rigid the membranes should not be ruptured, and if the patient had been admitted to the hospital for that purpose, she should be sent home to await the onset of labor. Such a patient will usually return to the hospital in labor about two weeks later. Caution exercised in this manner will help to avoid protracted labor and all the concern that goes with it.

DR. A. N. CREADICK, New Haven, Conn.—A discussion of this subject has an infinite number of ramifications, one of which I have not heard emphasized by the discussants and which I would like to call attention.

It is obvious that a multipara with a partially dilated cervix, at term and with the head engaged, had better be brought into the hospital. The anesthetist had better be available because when you rupture the membranes delivery will be immediate. On the other hand, when you get a stout patient with a thick neck, swayback, midpelvic contraction, with a long, hard cervix, and you begin to pick and pick and pick, you get into trouble. I have seen my juniors make trouble for themselves and raise fetal mortality and maternal morbidity. It is those women who have indolent uteri, whose expulsive forces are inadequate, whose uteri are not readily irritated, who will have prolonged labors which are dangerous to the fetus. In 1915, Dr. Slemmons showed how the organisms penetrated the amniotic cavity. In 1922, I showed how the same organisms traversed the cord and gave the fetus a septicemia, and I recovered the organisms from the cord and from the empyema in the baby. That was accompanied by intrapartum fever.

## PRIVATE CASES (INCLUDING CONSULTATIONS) FROM NOVEMBER, 1932, TO AUGUST, 1946

	NO. OF CASES	NEONATAL DEATHS	STILLBIRTHS	FETILE PUPERUM	ECLAMPSIA	TOXEMIA	ABLATIO PLACENTAE	DETACHED RETINA	INVERSION OF UTERUS	SHOCK	PROLAPSED CORD	POSTPARTUM HEMORRHAGE	PHLEBITIS	CONSTRUCTION RING	PLACENTA PREVIA	TWINS	MATERNAL DEATHS
Total	6,183	146 (2.2%)	154 (2.4%)	315 (5.0%)	24	106	61	4	3	12	29	58	19	125	93	37	6
Amniotomy	4,045	56 (1.1%)	47 (1.1%)	160 (3.9%)	11	75	23	3	2	6	8	35	7	75	35	15	4
All others	2,138	90 (4.2%)	107 (5.0%)	155 (7.2%)	13	31	38	1	1	6	21	23	12	50	58	22	2
																	Heart disease, congestive heart failure Pre-eclampsia Steiner's disease Placenta previa Sepsis, pneumonia Ruptured uterus, hysterectomy, pneumonia

So I think these figures show that in carefully selected cases where you know the history and you have the measurements of the baby and the feel of the cervix to guide you, induced labor can be safely done. I agree with the essayist's conclusions about long labors. The figures, however, show that amniotomy at or near term can be done comparatively safely.

DR. J. BAY JACOBS, Washington, D. C.—I am probably in the same predicament as Dr. Rucker. I have not induced labor in as many women, but have done so over a long period of time. Dr. Roblee's presentation is timely and represents a good deal of work. I do not feel that the induction of labor in properly selected cases is too unwise, nor do I look for the death of the mother or fetus as a result of it. Ordinarily, I am no more concerned than if the patient had started in labor of her own accord.

Dr. Colvin's discussion was very practical. I believe we are all of the same opinion except that the incidence of morbidity, in his experience, seems rather similar to that of the essayist. I am sure that the frequency of morbidity, either maternal or fetal, in my experience is no greater than that of any comparable number of cases permitted to start in labor spontaneously and managed by the average man. I have noted no difference in morbidity between cases that I induce and those that go into labor spontaneously.

If cases were not carefully selected for induction, one would expect the general trend of results to be similar to those reported by the essayist, especially if they were induced by a large group of men, many of them not trained obstetricians. From that point of view, Dr. Roblee's results are not unexpected and not surprising.

A word might be said about the means of inducing labor. Of course, the bag and bougie are out of date, in my opinion. I see no indication for using them. Before the war, when quinine was available, I used to resort to a dose of castor oil, later followed by an enema and then small doses of quinine. Several hours later, I would rupture the membranes. There appeared to be no ill effects, although the use of an excessive amount of quinine is not justifiable. During the war, when quinine was not available, we soon found that merely a dose of castor oil, an enema, and rupture of the membranes at the proper time, and in properly selected cases, were satisfactory.

As to the duration of labor, it seems to be shorter than when labor starts spontaneously. Occasionally, one might encounter a protracted labor, but if the cases were selected with due caution, the incidence would probably be no greater than would ordinarily occur in any series of cases that were not induced.

I wish to thank Dr. Creadick and Dr. Hamilton for their remarks and discussion. One criticism which could have been made was that in some of the charts insufficient numbers were recorded to permit of dogmatic conclusions. However, regardless of the groupings in all cases, the averages showed that nonmorbid patients had shorter hours of labor with above average or average birth weights for the babies; whereas the morbid patients showed longer hours of labor with lower than average birth weights for the babies. This means that the nonmorbid patients were at the threshold of labor when induction was instituted.

One last point. It so happens that three patients at the St. Louis Maternity Hospital were being studied as to their sodium pregnandiol glucuronidate excreted in the urine. Induction of labor in these cases was a failure until repeated efforts coincided with a fall of NaPG of 70 mg. to a 10 mg. excretion; confirming the work of Lyons, and also substantiating the forty-eight hour interval of incidence of failure to induce as shown in these charts.



DR. MILTON SMITH LEWIS, Nashville, Tenn.—I have had the opportunity to observe 500 private patients in whom labor was induced by the artificial rupture of the membranes: 461 cases were induced for the reason that they were at term and the "cervix was ripe" with two or more fingers' dilatation. The remaining 39 cases were induced in a similar manner for definite medical indications.

I am in complete accord with Dr. Jacobs that in properly selected cases artificial rupture of the membranes entails no serious increased risk to the mother or infant other than to be expected in a comparable group of natural labors. However, we do not believe that the routine rupture of the membranes should ever be employed just for the convenience of the patient or physician. But if the above criterion is strictly adhered to we are of the opinion that it is a simple, effective method of inducing labor.

It was interesting to observe that the latent period, from the time of rupture of the membranes to the appearance of definite uterine contractions, was less than one hour in 35 per cent; less than two hours in 36 per cent; less than four hours in 24 per cent. Or, in other words, 85 per cent, both primiparas and multiparas, had a latent period of less than four hours. Fifteen per cent had a latent period from six to twelve hours. Only one patient in the entire series had a latent period of more than twenty-four hours. We do not advocate the use of pituitrin after the rupture of membranes, however, we did use it in 11 instances where the pains were not as effective as we thought they should be.

Labor was definitely shortened; 36 per cent delivered in less than three hours; 39 per cent from three to six hours; 20 per cent from six to twelve hours, and 3 per cent from twelve to twenty-four hours. Only one patient had a labor of more than twenty-four hours. This was a case of uterine inertia in an occipitoposterior position, although she had a latent period of three hours.

Delivery was spontaneous in 45 per cent. Low forceps were used in 51 per cent; eleven required midforceps, and twelve labors were terminated by breech extraction.

There were no stillbirths. However, there were three neonatal deaths that occurred from twenty-four to forty-eight hours following delivery that were due to congenital atelectasis or, if you wish, pneumonia of the newborn, found at autopsy. All three were delivered spontaneously.

The total morbidity rate based on a reading of 100.4° F. at any time excluding the first twenty-four hours was three, or 0.6 per cent.

The incidence of laceration of the cervix observed at the six weeks' postpartum examination was 61, or 12.2 per cent. Twenty-one of these were repaired following a subsequent delivery.

The artificial rupture of the membranes in selected cases is a very useful method for the induction of labor, and the mortality and morbidity for the mother and infant can be kept exceedingly low.

DR. BUFORD C. HAMILTON, Kansas City, Mo.—Suppose a moratorium was declared on all unnecessary obstetric interference at this time. I think we will agree that for some time we have had a national obstetric interference inflation. Dr. Roblee has attempted to show us the dangers of induction of labor, and I know this is not his work or a reflection of his work. I am familiar with my own pathologic results in the induction of labor. I am also certain that others have had the same results.

DR. ROBLEE (Closing).—Dr. Holman will find the answer to his question in regard to relative morbidity of medical and surgical induction of labor as pointed out in these charts. Unlike Dr. Holman's series, these cases were not one doctor's, but were both ward and private patients of at least ten different men.

Dr. Rucker has shown low morbidity with induction of labor, but case selection is the answer. Dr. Jacobs induces only such cases in which there are no contraindications and in which there is cervical dilatation with head engagement. In my opinion these patients would have gone into labor within the next forty-eight hours without induction.

its effect. Such a procedure entailed a good many technical difficulties both from the standpoint of bacteriology and roentgen-ray administration. These problems were overcome through the advice and invaluable assistance of Paul F. Clark, Professor of Bacteriology, and Ernst A. Pohle, Professor of Radiology.

Dogs of comparable physical make-up were selected, and each weighed about 12 kilograms. The selection of these dogs was particularly important from the standpoint of roentgen-ray administration.

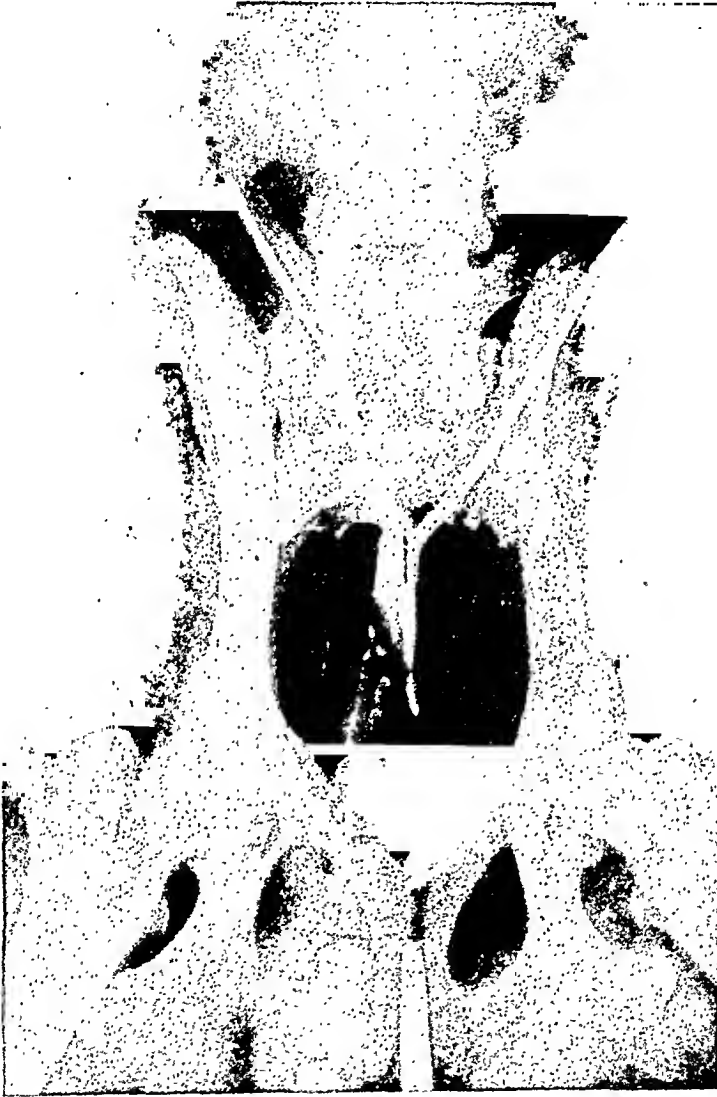


Fig. 1.

A strain of attenuated bovine tubercle bacilli was selected, which tended to produce localized nonprogressive lesions which appeared suitable for this research.

As to the choice of tubercle bacilli (human or bovine), the difference in reaction would be purely relative which should not materially alter any experimental conclusions.

Fig. 1 shows a normal uterus of a dog which has been injected with lipiodal and x-rayed.

# THE TREATMENT OF PELVIC TUBERCULOSIS IN THE FEMALE BY RADIATION THERAPY BASED UPON EXPERIMENTAL EVIDENCE IN THE ANIMAL AND CLINICAL RESULTS IN THE HUMAN\*

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THE treatment of pelvic tuberculosis in women, which lends itself to medical, surgical, or radiologic considerations, has been subjected to considerable controversy.

It is the purpose of this paper to consider the radiologic aspects of therapy in this disease relative to experimental studies in the animal and clinical investigations in the human.

Roentgen-ray therapy for genital tuberculosis was introduced by Bircher in 1908. According to the original report of Bircher, roentgen-ray therapy is indicated primarily (a) in those cases with adhesive or plastic peritoneal tuberculosis in which operation offers but little help, (b) in cases with cachexia in which operation is contraindicated, (c) in cases which refuse operation, and (d) in slight and benign cases. Cases in which roentgen-rays are to be used secondarily include (a) those in which the exudate reappears soon after operation, and does not disappear within fourteen days, and (b) all cases in which the symptoms return after operation.

Among the many reports favoring this type of therapy—alone or combined with surgery—may be mentioned Bumm, Krönig, and Zweifel in Germany; Schauta in Vienna; Solomons in Ireland; and Ford, Polak, and Jameson in the United States.

Since Bircher's original paper, Martius, Kolischer, and Gibert feel that roentgen-ray therapy should be extended to include all types of pelvic tuberculosis. While others, such as Edling, Weibel, and Pestalozza believe roentgen-ray therapy has its greatest indication as a postoperative measure following conservative or radical surgery. This group does not feel that it is a question of the roentgen-rays versus surgery, but a combination of the two methods.

The antagonist contends that radiation therapy of pelvic tuberculosis in the human is of no great therapeutic value and leads to (1) dissemination of the tuberculous process, (2) fistulous tract formation, (3) intestinal obstruction, and (4) that lymphocytic destruction by the roentgen rays leads to a breakdown in the healing process. It occurred to me that some of these criticisms might be answered by our findings at the University of Wisconsin General Hospital; not only by clinical observations of patients with this disease treated by roentgen-ray exposure in our clinic, but also by producing the pelvic disease in the laboratory animal and subjecting it to roentgen rays.

It was decided to produce pelvic tuberculosis experimentally in the female dog and subject these animals to roentgen-ray therapy in order to observe

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the uterine horns with methylene blue, and then completely freezing the dog. Following this procedure a pelvic section was made.

Twenty dogs were used in this investigation in which the tuberculous process was limited to the pelvis.

Table I shows the number of series administered to the dogs as compiled by the Department of Radiology. A series consisted of one treatment each week for six weeks. The interval between series was approximately one month.

Tables II and III show in detail the roentgen-ray therapy given to several of these dogs.

TABLE I

DOG NUMBER	NUMBER OF SERIES OF TREATMENT
2	1
4	1
6	4
14	3
27	2
28	2
31	1 had only 5 treatments of first series. Too sick to finish. Died with sponge in abdomen.
33	1
34	5
36	4
37	4
39	1
41	4
42	1
43	3
44	1
45	3
46	2
47	2
48	2

TABLE II

X-ray over pelvis; 50 r posterior—100 r anterior. Field approximately 8 by 5½ to 6 cm. varying with size of dog; 0.5 copper + 1 aluminum filter; 6 milliamper; 180 kilovolt; 50 cm. distance.

	43, 45	45, 43
SERIES I	II	III
1st treatment—5.21.34	7.23.34	10. 1.34
2nd treatment—5.28.34	7.30.34	10. 8.34
3rd treatment—6. 4.34	8. 6.34	10.15.34
4th treatment—6.11.34	8.13.34	10.22.34
5th treatment—6.18.34	8.20.34	10.29.34
6th treatment—6.25.34	8.27.34	11. 5.34

TABLE III

X-ray: 75 r on two anterior areas (pelvis and abdomen—150 r). Field: abdomen, approximately 17 × 7 cm., pelvis as in Chart II; 0.5 copper—1 aluminum filter; 6 milliamper; 180 kilovolt; 50 cm. distance.

SERIES I (33, 34, 36)	II (34, 36)	III (34, 36)	IV (34, 36)
1st treatment—3.12.34	5.21.34	7.23.34	10. 1.34
2nd treatment—3.19.34	5.28.34	7.30.34	10. 8.34
3rd treatment—3.26.34	6. 4.34	8. 6.34	10.15.34
4th treatment—4. 2.34	6.11.34	8.13.34	10.22.34
5th treatment—4. 9.34	6.18.34	8.20.34	10.29.34
6th treatment—4.16.34	6.25.34	8.27.34	11. 5.34

In the technique of injecting the dog's uterus with tubercle bacilli, the abdominal cavity was opened and both horns of the uterus were tied off at their distal ends by black silk, and a third strand of silk tied off the uterus from the vagina. The uterus was injected with a tuberculin syringe, and between  $\frac{1}{2}$  to 1 c.c. of the bacterial suspension was usually injected. The number of tubercle bacilli per field was found to be between 25 and 100. The opening at the site of the needle withdrawal was treated with phenol.

Fig. 2 shows a uterus of a dog which has been injected with tubercle bacilli, and demonstrates the marked enlargement of both horns and vaginal portion. There was also present a moderate amount of adhesive and exudative reaction. This specimen compared with Fig. 1 shows the marked pathologic changes macroscopically. A biopsy was positive for tuberculosis.



Fig. 2.

A second laparotomy was usually performed about two months after the initial injection, and the genital organs were inspected for gross signs of tuberculosis and confirmed by biopsy. Laparotomies were performed about every two months thereafter.

Interestingly enough in some instances, the pelvic pathology, following the infection, appeared to be the adhesive and exudative types, while in others the genital organs were perfectly free with little exudative reaction. In some cases there was undoubtedly a secondary inflammation. Only cases in which the disease was confined to the pelvis were used in this series.

Roentgen-ray therapy was instigated at different time intervals relative to the diagnosis and extent of the disease in order to make the investigation more complete.

It was necessary to determine accurately the x-ray distance for roentgen therapy in an average size dog. This was done by killing a dog, injecting

In analyzing the results of these dog experiments it is undoubtedly clear that roentgen ray was beneficial in the therapy of pelvic tuberculosis. It is interesting to note that only one dog died while under therapy. In the whole series of twenty dogs inoculated and treated by x-ray, there was no doubt that radiation therapy tended to limit the disease to the pelvis, had a direct effect upon the absorption of the exudate, and reduction of the secondary inflammation. There is every reason to believe that many of these dogs might have developed intestinal obstruction if x-ray had not been given to the pelvis and obviated the factors which produce intestinal obstruction. Some of these animals had as many as eight laparotomies, and only in one instance was a fistula formed. The abdominal wounds healed rapidly with only an occasional superficial infection.

In comparing the control series with those treated by roentgen-ray therapy and the beneficial results obtained in the latter, the results are conclusive.

The favorable results obtained in the foregoing experimental data which were carefully scrutinized, not only by myself, but by Dr. John W. Harris, led us to believe that, contrary to the previous condemnation of the use of x-ray in the treatment of pelvic tuberculosis in the female, we should reconsider its use. We have therefore, been using roentgen-ray therapy in the treatment of pelvic tuberculosis in the female.

Out of the cases treated by roentgen-rays, I have selected those which I felt were most representative. In reviewing the case histories, I shall confine my reports to those facts which are considered pertinent and exclude irrelevant data, tending to maintain clarity with brevity.

### Case Reports

CASE 1.—A. P., aged 19 years, Indian, was admitted to the hospital on Dec. 30, 1942. This patient had been hospitalized at the Hayward Indian Hospital on March 23, 1942, and the accompanying history from this institution showed that, dating from the birth of a child eighteen months previous to the time of her admission, the patient had been troubled with a vaginal discharge. On admission she complained of pain in the lower abdomen. She also had a small draining sinus lateral to the anal opening on the left buttock. Her physical examination at this time was essentially negative, except for lower abdominal tenderness on both sides. All laboratory tests were reported negative for the gonococcus and acid-fast organisms. The x-ray of her chest was negative, as were the agglutination tests. Her Wassermann was negative. Her temperature range was from 99.2° to 101.2° F. It was suggested by this institution that this patient have a complete gynecologic work-up. She was, therefore admitted to our service in the University Hospital and finally transferred to the tuberculosis service.

The following data were obtained while on our service: It was found on pelvic examination that the patient had a large right-sided pelvic mass which extended two fingerbreadths above the symphysis pubis with a mass of like size to the left. The uterus could not be separated from these masses. The vaginal secretions were cultured and found to be positive for tuberculosis. The tuberculin test was also positive. A piece of tissue taken from the anal fistula was also positive for tuberculosis. Repeated cervical, urethral, and vaginal smears were all negative. The Frei test was negative. Sedimentation test showed a graph

Fig. 3A shows a considerable enlargement of both horns and vaginal portion of the uterus after injection. There was a slight amount of exudative and adhesive reaction present. Roentgen-ray therapy was started at two months. Twenty-four exposures were given with monthly intervals between series. At the end of a year a most remarkable result can be observed when Figs. 3A and 3B of dog 34 are compared. Microscopic sections from 3B showed no tuberculosis. The results shown in this dog, both before and after x-ray treatment, were representative of the series.

Eight control dogs were inoculated with bovine tubercle bacilli and given no roentgen-ray therapy. Four of the dogs succumbed rapidly to the disease within a period of seven months after inoculation. These rapid deaths were due not only to the disease itself but were hastened by starvation. The dogs that were given deep x-ray therapy appeared to take their food much better and their weight was maintained at a higher level. Two dogs died at nine



Fig. 3.

and ten months, respectively, after their injections. One dog, apparently doing well at the end of thirteen months after the initial inoculation, had microscopic evidence of tuberculosis, even though the pelvis looked clear and the weight had been maintained. This dog was anesthetized at sixteen months, and sections of the pelvic organs showed an arrested tuberculosis. The eighth dog, sixteen months after the initial inoculation, had a pelvis which showed no microscopic evidence of tuberculosis. Four of these dogs in this series at autopsy showed a generalized military tuberculosis.

Of the twenty dogs that were inoculated, only nine could be carried over a two-year period because of the lack of space in the kennel and the demand for some of these dogs for use in the medical school for instructive purposes. Seven of the nine dogs showed an arrested tuberculosis, both by macroscopic and microscopic examination. The remaining two dogs still showed evidence of the disease.

CASE 3.—E. L., a 35-year-old parous woman was admitted to the hospital complaining of pelvic pain and a draining abdominal sinus which followed an indeterminate pelvic operation three years previously, at another institution. Her abdominal incision had opened and closed several times, draining considerable pus on several occasions before her admission to this hospital. Her menses were normal. Her temperature range was between 99° and 100° F. by mouth. Her hemoglobin upon admission was 54 per cent, and she was given 500 c.c. of citrated blood. Urine and blood chemical studies were normal. Wassermann was negative. Vaginal smears were negative. Smears and cultures from sinus tract showed *Staphylococcus albus*. Mantoux test after forty-eight hours was negative. Chest x-ray was negative. Barium enema was negative for intrinsic organic disease. This was given because of mucopurulent material in the stool; tuberculosis of the large bowel was also being considered. Pelvic examination showed a large mass filling the pelvis which was hard, nodular, and very sensitive. Pelvic findings at operation were a large inflammatory mass with the intestines knotted together by dense adhesions, the visualization of the pelvic organs was impossible. No line of cleavage could be found for the removal of the inflammatory mass. Microscopic examination of a biopsy taken at the time of operation was reported tuberculosis. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days in which the H.V.L. in copper equaled 1.0 mm. This patient was given another series of deep x-ray treatments with the same dosage four months later. A remarkable subsidence of the pelvic mass was shown at her periodic examinations. At the end of the year the pelvic examination showed an essentially clear pelvis. Interestingly enough, two years after the initial x-ray treatment had been given an abdominal sinus was still draining; this was excised. A progress note made seven months following this excision showed the abdominal wall to be well healed.

CASE 4.—G. J., aged 20 years, was admitted to the hospital on Dec. 5, 1935, complaining of abdominal pain and distention, general malaise, fever, nausea and vomiting, diarrhea, profuse night sweats, extreme toxemia, and a weight loss of twenty pounds since onset of the illness. Her history revealed no tuberculosis in the family. Her menses were normal. She had no leucorrhea. Her general physical examination showed her lungs to be normal. The x-ray plate of her chest showed no significant variations from normal on admission, however, three months later minimal tuberculous infiltration of left apex was reported. The sputum was negative to smear and culture, as was the gastric aspiration. Cultures for the tubercle bacillus were also negative. Her sedimentation test was that of an acute inflammatory process. Guinea pig inoculation was negative. Pelvic examination showed bilateral, fixed, stonelike masses in both fornices. The mass on the right side was about 10 cm. in diameter, while the left-sided mass was indeterminate as to size.

Fifteen days following admission, a laparotomy was performed. Upon opening the peritoneal cavity it was found that the intestines were bound down and involved in bilateral adnexal masses with adhesions involving the visceral and parietal peritoneum. There was a very slight amount of straw-colored, free fluid in the abdominal cavity. The uterus was normal, but was fixed by the inflammatory mass. The pelvic organs were studded with small, white, miliary nodules. It was impossible to do any extensive exploration because of the acuteness of the inflammatory process. Biopsies were taken of the nodules. The abdomen was closed. The microscopic examination of the nodules was reported as tuberculosis. Ten days following the operation it was decided to give the patient x-ray therapy. On three consecutive days the patient was given 100 roentgens, with the H.V.L. in copper equaling 1.0



of an acute inflammatory process. A stereo of the chest on Jan. 1, 1943, showed small bilateral pleural effusions with some pleural thickening and nothing in these studies to indicate the etiology by changes in the lung field. During her stay in the hospital, the patient's temperature fluctuated between 101° and 102° F. with pulse rate between 100 and 120. Following these examinations the patient was transferred on Jan. 18, 1943, to the sanatorium because of her acute toxic condition.

The patient was readmitted to the hospital on April 7, 1944, after a year of sanatorium care. At this time the patient was less toxic, with a temperature running between 99° and 100° F. and a weight gain of twenty-eight pounds. An x-ray of the chest on April 11, 1944, showed no pleural effusion. Some pleural thickening obliterating the sulci on both sides and some thickening of the secondary interlobar fissure on the right, no positive parenchymal infiltration. The masses previously described in the pelvis were still present and were somewhat larger. On April 21, 1944, the patient had a colostomy because of obstructive bowel symptoms. Beginning May 15, and for four consecutive days, the patient was given 200 roentgens, with the H.V.L. in copper equaling 1.05 mm. to the anterior and posterior pelvis.

On July 18, 1944, the patient showed a marked regression of pelvic masses, and the uterus was well outlined for the first time, being about twice the normal size.

On Sept. 15, 1944, and for four consecutive days, the patient was given another series of deep x-ray consisting of four doses of 200 roentgens each, with H.V.L. in copper equaling 1.05 mm. to the anterior and posterior pelvis. She was discharged from the hospital following this series.

She was readmitted on Nov. 10, 1944, at which time she was examined by the gynecologic clinic and found to have a uterus of normal size with no palpable masses. She was discharged on Nov. 18, 1944.

The patient was readmitted on Feb. 6, 1945, at which time she was re-examined with the findings as follows: The large masses originally described had melted away and the fornices were clear. The uterus was normal, lying in the horizontal position, and the lesion about the rectum appeared to be healing. The results following deep x-ray to the masses were reported as remarkable.

CASE 2.—J. L., a 22-year-old, nulliparous patient developed pain in both lower quadrants. Temperature prior to operation was 99° to 100° F. by mouth. Weight was 100 pounds, a weight loss of ten pounds. The x-ray of the lungs was negative. The Wassermann was negative. Urine, blood, and blood chemical studies were normal. Pelvic diagnosis was bilateral cystic ovaries. Abdominal and pelvic findings at operation were free fluid in pelvis and abdomen; a plastic exudate was noted over the parietal and visceral peritoneum, adnexa, and uterus. The pelvic organs were one conglomerate mass with no possibility of surgical removal. The peritoneal fluid was taken for culture and staining; these were found to be negative. Biopsy of tissue removed from the mass was positive for tuberculosis. The patient was asked to return to the hospital in six weeks for x-ray administration to the pelvis.

Her first series of x-ray was 50 roentgen units on successive days for four treatments. In this series the H.V.L. in copper equaled 1.05 mm. This first series of x-ray was not a sterilizing dose and produced no pelvic improvement. Two months later, following her second series of x-ray treatments which totaled 800 roentgen units her pelvic mass began to disappear rapidly as shown by monthly examinations and she became more comfortable. This patient has a normal pelvis to palpation at the present time, approximately sixteen months following operation.

The patient was discharged Dec. 1, 1937, to return in six months as thought advisable by the sanatorium.

The patient returned to the gynecologic service on Aug. 16, 1938. She had developed some cough and, after checking her pelvis and abdomen, which were negative, it was thought advisable to exclude the chest from any activity. The tuberculosis service considered her chest findings as negative as was the x-ray of the chest. In view of a normal sedimentation rate she was discharged to be x-rayed every six months.

On Dec. 1, 1938, the patient gave a history of having had regular periods for the past few months and it was deemed necessary to give her another series of deep x-ray directed toward castration. She was given three deep x-ray treatments on three consecutive days of 200 roentgens, with H.V.L. in copper equaling 1.05 mm. The application was 100 roentgens to both the anterior and posterior pelvis at each treatment, giving a total of 600 roentgens.

The patient was again seen on February 28, May 16, and October 31, 1939. Up to this time her course had been uneventful with negative chest, abdominal, and pelvic findings. The total weight gain had been 59 pounds.

CASE 5.—F. L., aged 29 years, Indian, a patient on the Tuberculosis Service, with far-advanced pulmonary tuberculosis, was seen by the gynecologic service. Patient was acutely ill and running a temperature up to 101° F. Her complaints were, in part, a sharp pain, occasionally dull and throbbing, low down in the pelvis radiating into the limbs. She also complained of a similar pain on the right side. There was considerable leucorrhea. On pelvic examination this patient had a large, fixed, irregular mass about the size of an orange on the left side which extended somewhat posteriorly into the cul-de-sac. There was also a smaller mass present, on the right side. The uterus was normal and the cervix was clean. The impression was a tuberculosis of the genital organs. Smears were negative for gonococci and acid-fast organisms. Cultures gave no information. It was decided to do a diagnostic curettage with a suspension and culture of the endometrial tissues. These proved to be positive for tuberculosis, however, the endometrium on gross examination looked normal and was somewhat scanty. The pathologic report showed chronic cervicitis and early tuberculous endometritis. This patient was given four deep x-ray treatments of 100 roentgens, with H.V.L. in copper equaling 2.4 mm., two to the anterior pelvis and two to the posterior pelvis on alternating days. The patient was discharged to the State Sanatorium to return in six months.

In a telegraphic report from Dr. R. H. Schmidt, Superintendent of the State Sanatorium, dated Aug. 16, 1946, the findings were as follows: Patient has been afebrile dating two weeks following the x-ray therapy, complete relief symptomatically since May, 1946, with a marked regression of the pelvic masses. The right-sided mass measures 1½ cm. in diameter, and no mass is palpable in the left fornix. No menses since May.

CASE 6.—M. R., a 29-year-old, nulliparous patient was admitted to the hospital complaining of a tumor and pain in her right side. The patient's temperature was normal at the time of admission and remained normal throughout her hospital course. Her urine and blood chemical studies were negative. Wassermann was negative. Vaginal smears were negative. X-ray of chest was negative. Pelvic examination revealed a large right-sided tumor which was diagnosed as an ovarian cyst. At operation, large bilateral tubo-ovarian masses were found; both tubes showed a large hydrosalpinx and were studded with small miliary tubercles (see Fig. 4). The serous surface of the uterus

mm. to the anterior abdomen and pelvis. The patient was discharged from the hospital on Feb. 11, 1936, six weeks after the preliminary series of deep x-ray. At examination before discharge the abdomen was found to be less distended with a definite decrease in the right-sided mass and with the general condition of the patient greatly improved.

The patient was readmitted on March 16, 1936. During the interval in the sanatorium there had been little change in her abdominal symptoms, however, she did have some dull aching in the lower abdomen. On combined abdominal and pelvic examination the hard mass in the right fornix, which was continuous with the abdominal mass on that side, showed little change, however, the left fornix was now relatively free with only slight induration. The patient was given another series of three deep x-ray treatments of 100 roentgens, with H.V.L. in copper equaling 1.0 mm. for six days, every other day to the anterior right abdomen and the alternating days to the anterior left abdomen. She was discharged on April 6 to return in two months.

Patient was readmitted on May 26, 1936. At this time she was definitely improved over the previous admission, had gained five pounds in weight, had good color, her strength was greater, and she seldom had a sensation of fever. Combined abdominal and pelvic examination showed the uterus to be more freely movable. The nodular mass in the right lower quadrant showed no regression, however, the abdominal mass above and continuous with it, was more nodular. The left fornix was clear. There was no evidence of free fluid. In short, the pelvis was freer than before, but the upper abdomen remained the same. Consequently the patient was given another series of three deep x-ray treatments over the anterior abdomen using the same dosage and quality of radiation as used previously. The patient was discharged on June 3, 1936, to return in three months.

The patient was again admitted on Sept. 1, 1936, at which time she had gained eleven pounds in weight since her last discharge. At each previous discharge the patient had gone to a sanatorium and remained in bed, but during the last three months the patient had been gradually increasing her activities, having had no temperature rise except for one occasion. There had been some increase in pulse rate. At this time there was little change in the pelvis or abdomen on combined examination.

The patient returned to the outpatient department for a check-up on Nov. 1, 1936. At this time she gave a history of having had a normal menstrual period on Oct. 10, 1936, with a slight amount of pain. The patient still was continuing to gain weight and strength. The mass formerly present in the right fornix was no longer palpable. The uterus was anterior, of normal size, and freely movable. The left fornix was clear. The nodular mass was still palpated abdominally just below the umbilicus and was the size of a large orange.

On Jan. 12, 1937, the patient was again seen in the outpatient department, feeling very well and having no complaints. She had menstruated twice in November and once in December, scant amounts without pain. Combined abdominal and pelvic examinations showed no masses.

On March 16, May 18, and July 20, 1937, the patient returned to the outpatient department. She was feeling very well and had no complaints. She was having regular menses. No abdominal or pelvic masses were noted. She returned on Nov. 23, 1937; the pelvic was essentially clear with no evidence of pelvic mass and nothing could be felt on abdominal examination. It was decided at this time to give her a sterilizing dose of deep x-ray. The patient was therefore admitted to the hospital and given three treatments of 100 roentgens with the H.V.L. in copper 1.0 mm. to the anterior right abdomen every other day and to the anterior left abdomen on the alternating days.

### Summary and Conclusions

Roentgen-ray therapy, by producing a temporary or permanent castration, tends to conserve the patient's blood and undoubtedly adds to her resistance. This is particularly important in the anemic patient.

Jameson has pointed out that it is a well-recognized clinical observation that tuberculous women are unfavorably affected by their menses. The cough becomes more severe and distressing, the expectoration may be increased, and dyspnea more marked. Examination of the lungs at this time usually shows increased physical signs, and sudden changes in the progress of the disease are likely to occur.

By analogy it seems logical that due to the increased activity and vascular changes in the pelvis at the time of the menses, a deleterious effect would be produced upon the pelvic tuberculosis as is produced in the lung. In fact, temporary or permanent castration by roentgen rays in the pelvic tuberculosis may be a blessing in disguise.

The x-ray dosage as carried out in this series is not large enough to have a profound effect upon the white blood cells, and I cannot agree that it interferes with healing. However, it is a well-known fact that x-rays do stimulate the production of young fibroblasts which is most important in the conversion of tubercles into fibrous tissue.

Roentgen rays are useful in reducing secondary inflammation and infection which is important in the healing of a tuberculous process.

There is no real evidence as substantiated by these studies that fistulas, dissemination of the tuberculous process, intestinal obstruction, and perforation of a viscus are serious complications of roentgen-ray therapy. In fact, I have cured one fistula of tuberculous origin by deep x-ray therapy. It may also be said that deep x-ray therapy is useful in the absorption of exudates and the reduction of secondary inflammation and infection, thereby tending to relieve and prevent intestinal obstruction.

I feel that failures of roentgen-ray therapy as used by the early observers were due to unwarranted dosage with improper spacing. The ideal dosage is one that produces temporary or permanent castration; I tend toward the latter. As Dr. J. M. Wilkie has pointed out, the physiologic age is increased by castration which acts favorably toward the healing of tuberculosis in general. I emphasize the fact that healing of the pelvic disease may favorably effect the healing of this disease elsewhere, and, also, the disease elsewhere may unfavorably effect the progress of the pelvic disease. The more active the tuberculous process, the less favorable will be the prognosis.

In this series it can be stated that roentgen-ray therapy gave excellent cures in most cases, and it must be emphasized that x-ray therapy is an important adjunct following surgery.

The diagnosis of pelvic tuberculosis is usually made at laparotomy. If the pelvic disease can be diagnosed by such procedures as curettage, including suspension and cultures of endometrial tissue, endometrial biopsy, and exami-

was also studded with miliary tubercles, as was the serosa of the intestine. The ovaries were also involved in the tuberculous process. A bilateral salpingo-oophorectomy and supravaginal hysterectomy was performed. A biopsy was diagnosed tuberculosis. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days. The H.V.L. in copper equaled 1.0 mm. Three months following the above series of x-ray treatments, 100 roentgen units of x-ray were given daily for four days. The H.V.L. of copper was the same as the previous treatments. The patient returned every two months for examinations for approximately a year following operation. Her pelvis was always essentially negative.

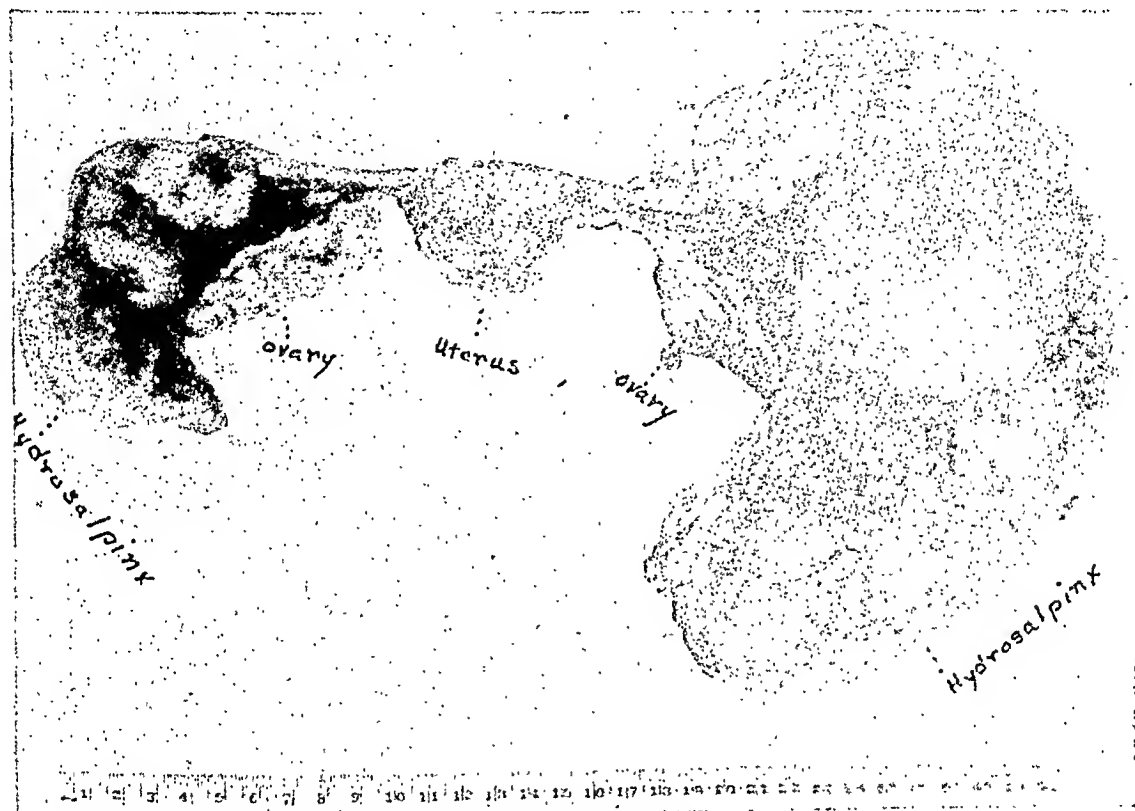


Fig. 4.

CASE 7.—E. C., a 42-year-old woman was admitted to the hospital complaining of pain in the left side which was aggravated at the time of the menses. Her menses were normal except for the pain. Urine and blood chemical studies were negative. Wassermann was negative. Vaginal smears were negative. X-ray of the chest was normal. The sedimentation time was slightly active. Pelvic diagnosis was fibromyomata uteri and right ovarian cyst. Findings at operation were that both tubes showed a large bilateral hydrosalpinx; both ovaries were twice normal size and cystic; the uterus was three times normal size but symmetrical. A bilateral salpingo-oophorectomy and supravaginal hysterectomy were done. Pathologic report was tuberculosis of the tubes, ovaries, and uterus. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days. The H.V.L. in copper equaled 1.0 mm. Two months following the above series of x-ray treatments, 75 roentgen units were given daily for three days. The H.V.L. in copper equaled 1.0 mm. This patient appeared for examinations every two months for more than a year. Her pelvic findings were negative at all times.

DR. W. WAYNE BABCOCK, Philadelphia, Pa.—This paper brings to my mind experimental work that was taking place in 1890. At that time doctors were journeying to Dr. Koch's laboratory in Germany where he injected experimental animals with tubercle bacilli, produced a localized tuberculosis, and then injected tuberculin, when the lesions melted down, discharged, and the animals promptly recovered. The visiting doctors returned home and indiscriminately used the treatment on their tuberculous patients. Large tuberculous pulmonary consolidations melted down, obstructed the bronchi, with suffocation; or other fatal results followed the therapeutic use of tuberculin and it was largely abandoned. Having seen in New York some of the early dramatic results in patients with lupus, I was led to use a mixed bovine and human tuberculin for surgical tuberculosis, and some of the results obtained have been spectacular. A recent example was in a man referred for the operative removal of a rapidly enlarging and very much indurated breast, diagnosed as sarcomatous. From the injection of  $\frac{1}{4}$  minim of the mixed tuberculins there was a marked reaction. The breast became very red, hot and swollen, and soon softened, so that the liquefied contents could be evacuated through a small incision. Several additional injections were given, and at the end of two months the breast appeared normal. Similar results have been obtained with tuberculous collections in the abdomen and pelvis. One woman with pelvic tuberculosis, rectovaginal fistula and involvement of the anterior abdominal wall had had eleven unsuccessful operations during a period of twelve years. After a series of tuberculin injections the fistula was closed and the patient has remained well for nine years. From these and other apparent cures I feel that tuberculin should be reconsidered. However, patients treated should be selected carefully and be free from any extensive disease of the lungs or central nervous system. After testing, massive doses should be used, with intervals of rest to carry the patient well over the negative phase. As the tissues often are unable to absorb the liquefied tuberculous material, evacuation by aspiration or incision is often necessary.

DR. JAMES A. CORSCADEN, New York, N. Y.—I would like to extend this discussion to the treatment of fibroids complicated by pelvic inflammatory disease and reduce the mortality from about 8 per cent in such cases to zero. I am speaking of the pyogenic infections as well as tuberculosis. We have a series of some 20 cases of fibromyoma complicated by pelvic inflammatory disease so treated. In 12 of these, operations had been attempted and abandoned because of technical difficulties. In all of them the abnormal bleeding stopped in 75 per cent of them, subjective symptoms (pain) subsided, and in all the mass diminished in size. These principles can be applied to cases of either tuberculosis or pyogenic infections. The essential factor is the proper dosage.

nations of vaginal secretions, then pelvic tuberculosis should be treated exclusively by roentgen-ray therapy; however, without positive evidence of tuberculosis this treatment should be condemned.

I wish to thank Dr. James M. Wilkie and Dr. Helen Dickie of the Tuberculosis Service of the University of Wisconsin, for their invaluable assistance and cooperation.

### Discussion

DR. HERBERT E. SCHMITZ, Chicago, Ill.—This interesting and scientific study carried on by Dr. Campbell and his associates demonstrates conclusively the value of x-ray therapy in the treatment of pelvic tuberculosis. We should feel deeply grateful to him for bringing these facts before our Society. The literature bears definite proof of long years of neglect of irradiation therapy, due to the gynecologists' training in the surgical management of this disease. That this latter method is faulty is evidenced by an operative mortality rate of 7 to 8 per cent and an occurrence of postoperative fistulas in from 5 to 10 per cent. These figures are based on numerous case reports found in the literature.

In Dr. Campbell's animal study he had few complications arising as a result of x-ray therapy. In all 20 dogs treated in this manner the disease remained limited to the pelvis, and a direct effect upon the absorption of the exudate and reduction of the secondary inflammation was observed. In some cases as many as eight operations were performed on the animal, and in only one case did a fistula form.

Although Dr. Campbell believes an amenorrheic dose of x-ray to be most satisfactory, his Case IV had "negative findings" before the dosage had brought about this effect. In Cases VI and VII a bilateral oophorectomy was performed as part of the surgical therapy, and x-ray therapy could have acted only in clearing up or preventing residual granulations. That this is the action of x-ray therapy on pelvic tuberculosis is the general opinion of the radiologists, and the present dosage advocated by the majority of radiologists is a 5 to 50 per cent E.S.D.\* According to McIntosh, the average dose advocated by numerous workers seems to be 10 to 15 per cent E.S.D.,\* repeated weekly two to four times, and in several cycles at monthly or longer intervals. This dosage has recently been shown by Glenn of Duke University to elevate the phagocytic indices of rabbits. He found that if 100 roentgens (air) delivered at 140 kilovolts were given to rabbits the phagocytic titer between the first and fourth day showed a significant rise. Higher dosage or 200 kilovolts was only half as effective. He could not conclude as to whether or not the effect of irradiation is on the antibody producing mechanism, on the leucocytes, or on the plasma, or is a result of denaturation of local tissue proteins.

Our technique has varied little since it was first published by Henry Schmitz in 1925. Using 140 kilovolts at 50 cm. focal skin distance 150 V (air) are given to an anterior field. The size of the field is governed by the extent of the disease. This dosage is repeated to a posterior field three days later and this cycle repeated at weekly intervals until four such exposures have been given. A repetition of this dose is administered only if the absorption ceases and there is residual disease. Castration is not our primary object. If Dr. Campbell were to treat some of his animals with bilateral oophorectomy alone he would answer for us the role of castration in the treatment of pelvic tuberculosis.

In summarizing the use of x-ray in these cases I would suggest its use in tuberculosis of the endometrium with no symptoms referable to the tubes. I am acquainted with the high incidence of tubal involvement.

In frankly diseased tubes I would suggest surgical removal of the diseased adnexa followed by x-ray to prevent recurrent granulations.

In advanced cases I favor surgical procedures to confirm the diagnosis and to remove fluid and necrotic tissue. X-ray therapy should be administered as soon as the patient's conditions permits her transportation to the therapy department. Dosages as advocated should provoke very slight reaction if any.

\*Erythema skin distance.



mice those who by a mutation were colored black were significantly prone to develop fibrosarcoma at the site of injection of methyl cholanthrene. The chromosomes carrying the gene which determined black hair color also carried a gene which determined the tendency to grow the fibrosarcoma. Both characters followed Mendelian laws in successive generations. In humans, many inherited characters have been observed and some 200 popularly described,<sup>6</sup> and a beginning has been made in the attempt to correlate these types with the tendency to contract cancer.<sup>7-10</sup> These observations are very suggestive and should stimulate a more intensive study of these factors.

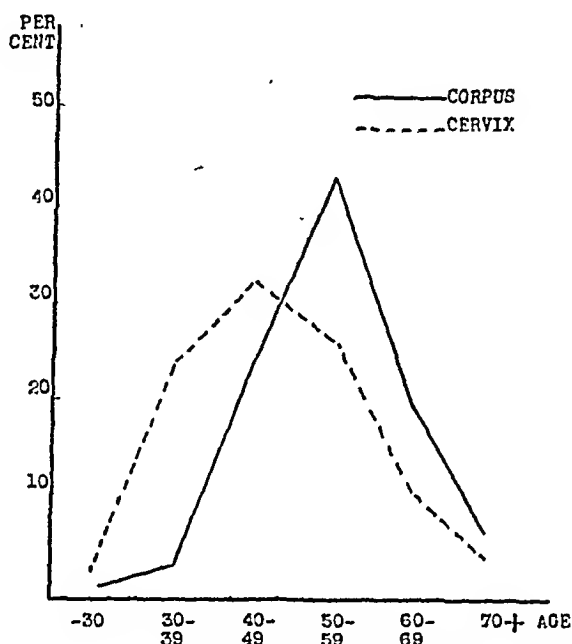


Fig. 1.—Percentage distribution of corpus and cervix cases falling within the different ten-year age groupings.

Our interest in this matter arose in the Sloane Tumor Clinic following a remark by Dr. Julius Gray that the women suffering from cancer of the corpus seemed to be much larger and heavier than those suffering from cancer of the cervix. Observations on age, race, weight, marital status, parity, and economic condition were routinely recorded on the charts. A study of these yielded some apparently significant data which are here presented as a preliminary to a more intensive study of patients who have contracted cancer in the hope that a plan may be outlined which could be used by several clinics in order that conclusions might be reached which would require a much longer time if made from observations in a single clinic.

For controls, the group of cases of cancer of the cervix was taken because it seemed interesting to compare the backgrounds of two malignant conditions in the same organ and because of the difficulty of establishing a norm for the general population in such matters as parity.

Fig. 1 shows the average age of women with carcinoma of the corpus to be 6.6 years greater than those with cervical cancer. This difference is less than is usually given. Study of race showed nothing in particular, except that there



## THE BACKGROUND OF CANCER OF THE CORPUS\*

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College of Physicians and Surgeons, Columbia University)*

OF THE many avenues through which the cancer problem may be attacked, that through the study of the individual in whom the cancer is to grow, is attracting increasing interest. From the practical standpoint, in the present state of our knowledge, the principal means by which cure rates can be raised is by decreasing the time lag between the onset of the disease and the application of therapy. The ability to identify the individual who is destined to contract cancer would enable us to bring her under close scrutiny or even institute prophylactic measures; in the case of the corpus uteri, prophylactic hysterectomy.

This hope is based on the idea that certain individuals are possessed of genes which determine characters which make them more liable to the development of cancer than their fellows, an idea which is acceptable to those who believe that cancer is not an acquired disease but is a condition resulting from the breaking down, distortion, or perversion of the laws which control normal cell growth. The normal cell is created, grows, functions, and dies. During its growth and while it remains active, it lives with its neighboring cells in a state of perfect balance so that none encroaches upon another. What maintains this equilibrium for so many decades is unknown but, like all biological processes, goes through its cycle and finally in these cases breaks down, allowing one cell or group of cells to grow lawlessly and encroach upon its neighbors, finally to become a definite cancer. Some individuals possess genes which determine controls so rigid that the normal balance is maintained to an advanced age. In others the control is so feeble that it breaks down early either spontaneously or under some carcinogenic influence.

In attempting to discover those individuals who are especially prone to contract cancer we may study their (1) heredity, (2) the coexistence of observable characters with the cancer tendency, (3) the pattern of behavior, and (4) those environmental factors which may instigate the cancerous process.

Heredity, from the experimental standpoint and from a study of humans, seems definitely to be a factor in the tendency to grow cancer.<sup>1-4</sup> But for practical purposes the study of heredity in an individual is rarely possible because of our reckless breeding customs and the lack of records of the occurrence of disease in and the causes of death of our ancestors.

A linkage between an observed character and one which determined a cancer tendency has been observed by Strong<sup>5</sup> who found that among brown

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

TABLE III. DIFFERENCES IN PERCENTAGE OF NULLIPAROUS WOMEN IN THE CERVIX AND CORPUS SERIES

	TOTAL NO.	PER CENT	DIFF.	+ P.E.	× P.E.
Cervix	524	16.6	22.0	± 2.61	8.43
Corpus	192	38.6			

Women with carcinoma of the corpus were more often nulliparous, 38.6 per cent of them having no children as against 16.6 per cent of the women having carcinoma of the cervix, Fig. 4 and Table III, a difference of 22.0 per cent  $\pm$  2.61, 8.43 times the probable error. Likewise, the percentage of infertile marriages among women with carcinoma of the corpus is unusually high; 30 of 81 women, or 37 per cent.

The economic status of women with carcinoma of the corpus is also exceptional, 145 out of 308, or 47 per cent, being private patients as against 182 of 765 patients with cancer of the cervix, or 23.8 per cent.

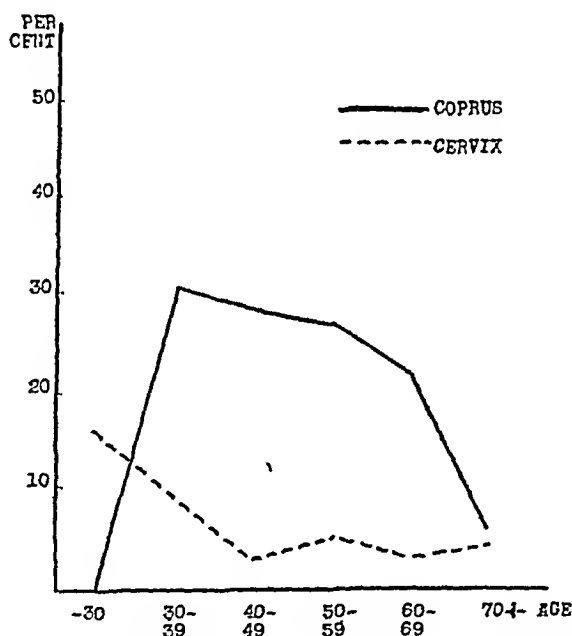


Fig. 3.—Percentage distribution of single women by age groups in the corpus and cervix series.

The menstrual pattern of these patients is also suggestive. Of 10 patients who developed carcinoma of the corpus prior to the menopause, five showed long-standing gross abnormalities of menstruation. Studies of the menopausal pattern in patients who later developed adenocarcinoma of the uterine corpus also revealed deviation from the normal. (a) The age incidence of cessation of menses was distinctly later than the 48-year average usually given—the peak menses was distinctly later than the 48-year average usually given—the peak incidence in our group coming in the 52- to 54-year range (Fig. 5). (b) The incidence of excessive and irregular bleeding during the menopause was greater in this studied group than in the general female population. Thirty-two patients, or 39 per cent, of the 82 who contracted the cancer after the menopause suffered from uterine bleeding abnormalities during the climacteric; this is three times the expected incidence of 13 per cent.<sup>11</sup>

were a proportionate number of Jewish women among those with cancer of the corpus, whereas among 765 cases of cancer of the cervix, there was only one in a Jewish woman.

The weight of the women with cancer of the corpus was significantly greater than that of women suffering from cancer of the cervix. Fig. 2 and Table I show a difference of 18 pounds, a difference nine times as great as the probable error, therefore significant although some difference is accounted for by the different average age. Many of these women not only were heavy but looked big, with heavy round hips and shoulders and small hands and feet.

TABLE I. MEAN WEIGHTS FOR CERVIX AND CORPUS SERIES

	NUMBER	MEAN	+ POSSIBLE ERROR	STANDARD DEVIATION
Cervix	348	140.30	$\pm 0.99$	27.40
Corpus	142	158.30	$\pm 1.76$	31.20
difference + P.E. $\times$ P.E. + 18.00 $\pm$ 2.02 8.91				

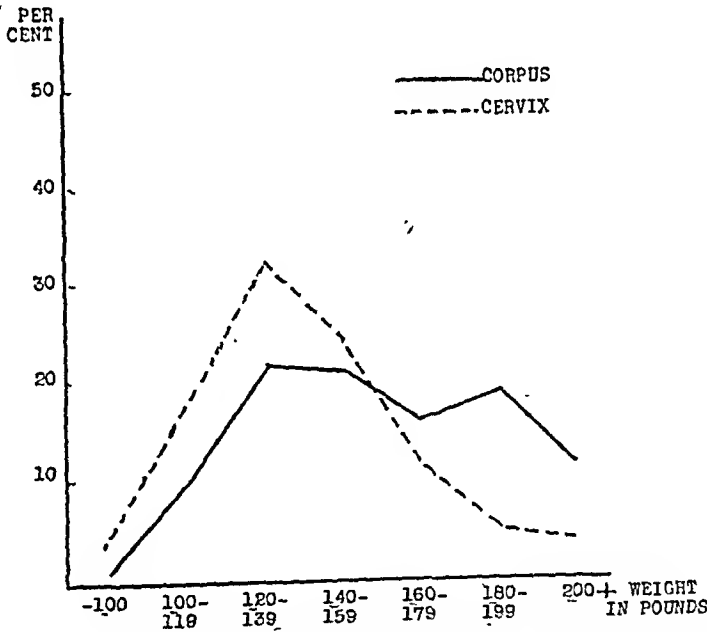


Fig. 2.—Percentage distribution of corpus and cervix cases falling within the different 20-pound weight groupings.

Women with cancer of the corpus did not marry as frequently as those with cancer of the cervix. Fig. 3 and Table II show that 24.8 per cent of 206 women with carcinoma of the corpus were unmarried as against 5.6 per cent of 550 women with cancer of the cervix, a difference of 19.2 per cent  $\pm$  2.13, or 9 times the probable error.

TABLE II. DIFFERENCES IN PERCENTAGE OF SINGLE WOMEN IN THE CERVIX AND CORPUS SERIES

	TOTAL NO.	PER CENT	DIFF.	+ P.E.	$\times$ P.E.
Cervix	550	5.6	19.2	$\pm 2.13$	9.01
Corpus	206	24.8			

The nature of this relationship between a menopause characterized by excessive bleeding and subsequent carcinoma of the corpus and a similar pattern of irregularity preceding cancer occurring before the menopause is not established; speculation concerning this pattern leads naturally to a study of growth stimulating substances involved in the sexual cycle, especially the estrogens.

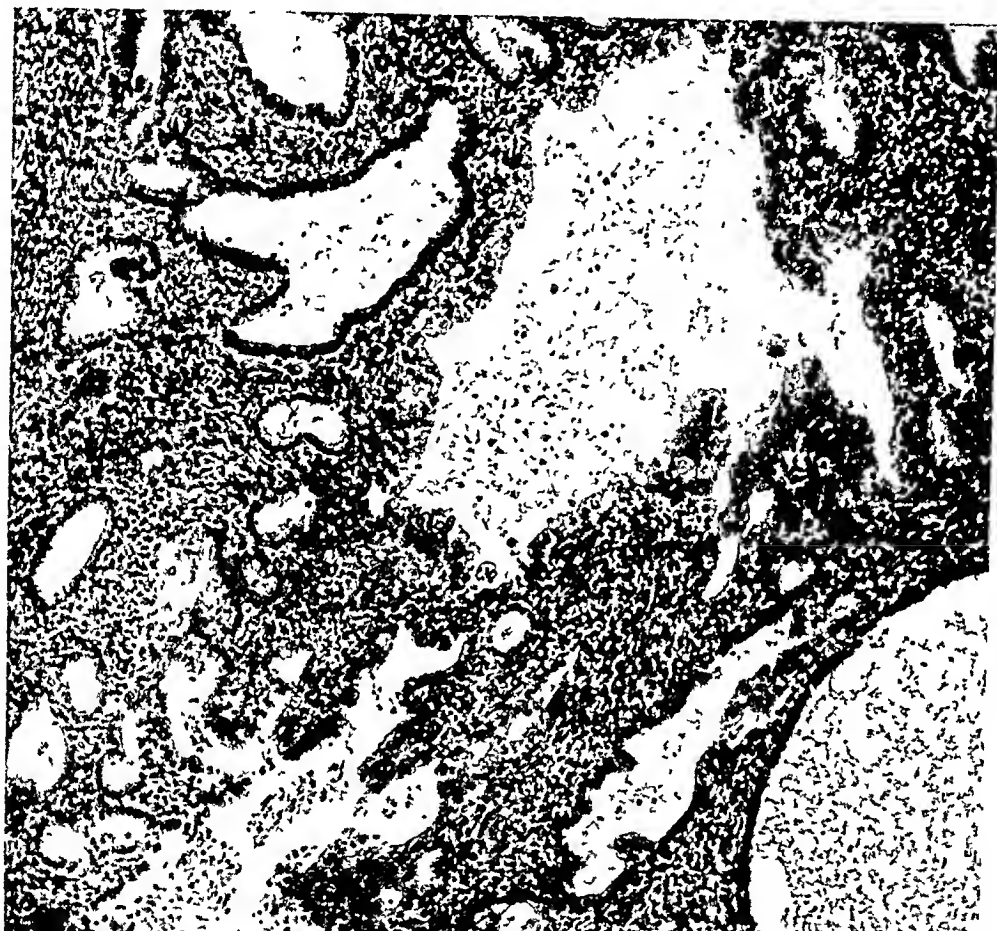


Fig. 6.—Endometrium of a postmenopausal patient after moderate estrogen stimulation, showing hyperplasia and epithelial activity.

We have collected data concerning the relation of unopposed estrogen stimulation and abnormal growth of the human endometrium, which we are now studying and will present later in detail. It is our purpose here to offer several fragments of evidence which suggest to us such a possible relationship. Many investigators have studied the effect of stimulating or inhibiting substances on high cancer strain mice, for example, which apparently possess this proper inherited substrate which makes for cancer susceptibility.

It has been well established that unopposed estrogen stimulation of the human endometrium will result in cystic glandular hyperplasia. We have found 31 per cent of uteri curetted for bleeding during the menopause to harbor hyperplastic endometrium. This condition may be the result of the patient's own endocrine imbalance, or it can be produced by the administration of estrogenic substances. In studying the background of patients who have

Further observation bearing on the question of the nature of the menopause and its relation to subsequent carcinoma was made on 1,100 women who had received a radiotherapeutic menopause for benign causes of bleeding and were followed for an average of 6.7 years.<sup>12</sup> Among them there were observed 15 cases of cancer of the uterus, which was three and one-half times as many

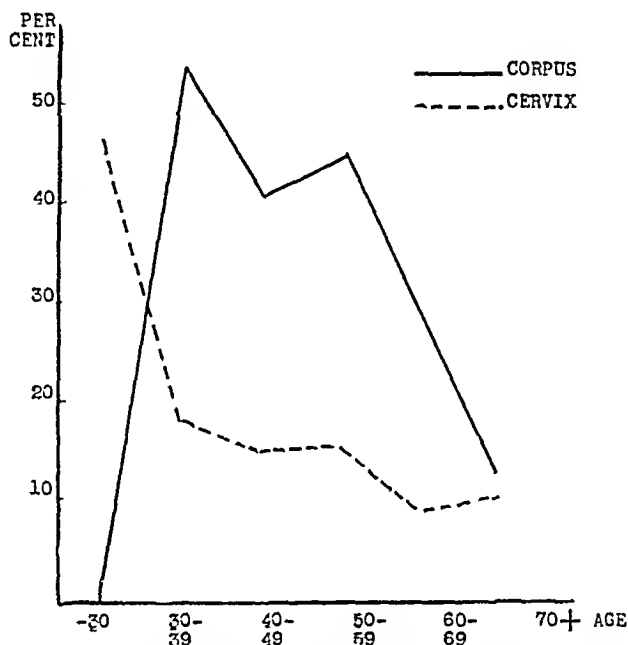


Fig. 4.—Percentage distribution of nulliparous cases by age groups in the corpus and cervix series.

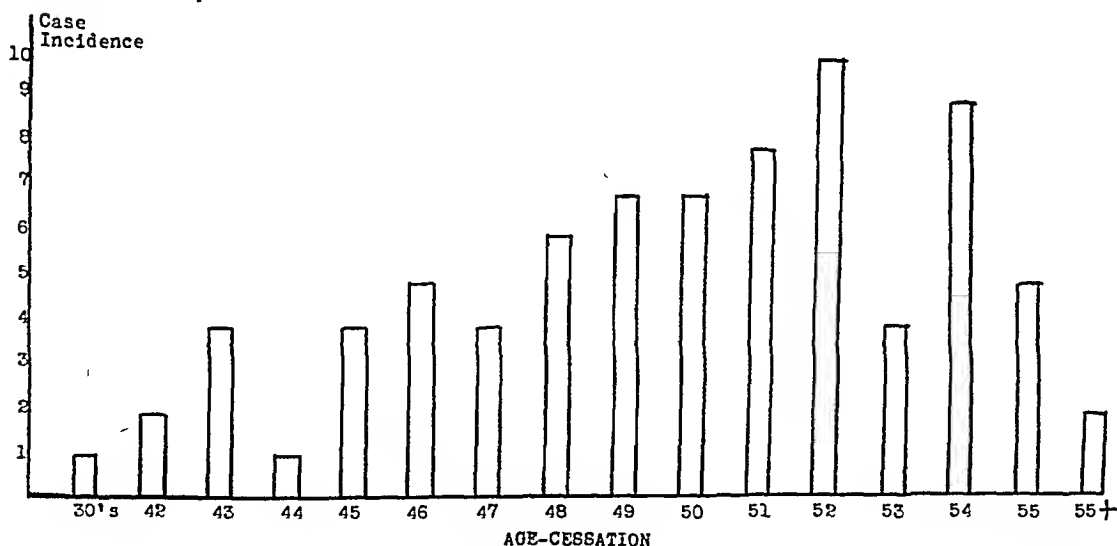


Fig. 5.—Age at menopause in patients who developed carcinoma of the corpus postmenopausally.

as would be expected in a similar sample of the general population. Nine of these were in the corpus and six in the cervix, the number in the cervix being what it should be; those in the corpus being three times the number to be expected. Randall<sup>11</sup> made a similar observation on a group of cases in whom there had been no radiotherapeutic menopause.

but this is merely a reflection of its low cost and the ease of its administration rather than the presence of any exceptional qualities. We have not found this response to be related to the quantity of the drug, but rather to the persistent stimulus. We have also studied five patients with corpus carcinoma, appearing after long-continued estrogen administration, whose histories are strongly suggestive of an etiologic relationship (Fig. 7). The histologic pattern of these adenocarcinomas in many instances bears a considerable resemblance to the hyperplastic and metaplastic endometria mentioned above. We also have collected three other corpus carcinomas whose development may have been accelerated by estrogen administration and their histologic pattern possibly modified. These data will be presented in a later communication.



Fig. 8.—Endometrium with marked hyperplasia and metaplastic areas suggesting adenocarcinoma.

The relation of hyperplasia of the endometrium to cancer has been debated for some time<sup>22-27</sup> without arrival at any conclusion. It is true that the gynecologic pathologist frequently sees hyperplastic endometria which suggest a stage in the development of carcinoma; he also sees corpus carcinomas with coexisting endometrial hyperplasia, and he sees hyperplastic endometrium curetted from postmenopausal women who later develop true adenocarcinoma. He will occasionally advise prophylactic hysterectomy for a patient with marked

developed corpus carcinoma, we do not find constant evidence of hyperplasia of the endometrium, but we have noted findings such as frequency of the bloody menopause, the delayed menopause, and increased incidence of sterility, all of which could be interpreted as evidence of endocrine imbalance; clinical phenomena sometimes associated with absent or infrequent ovulation. Curettage at other stages of the bleeding process in individual cases might raise this percentage of hyperplasia somewhat, for there is, undoubtedly, repeated building up and sloughing off of this tissue.

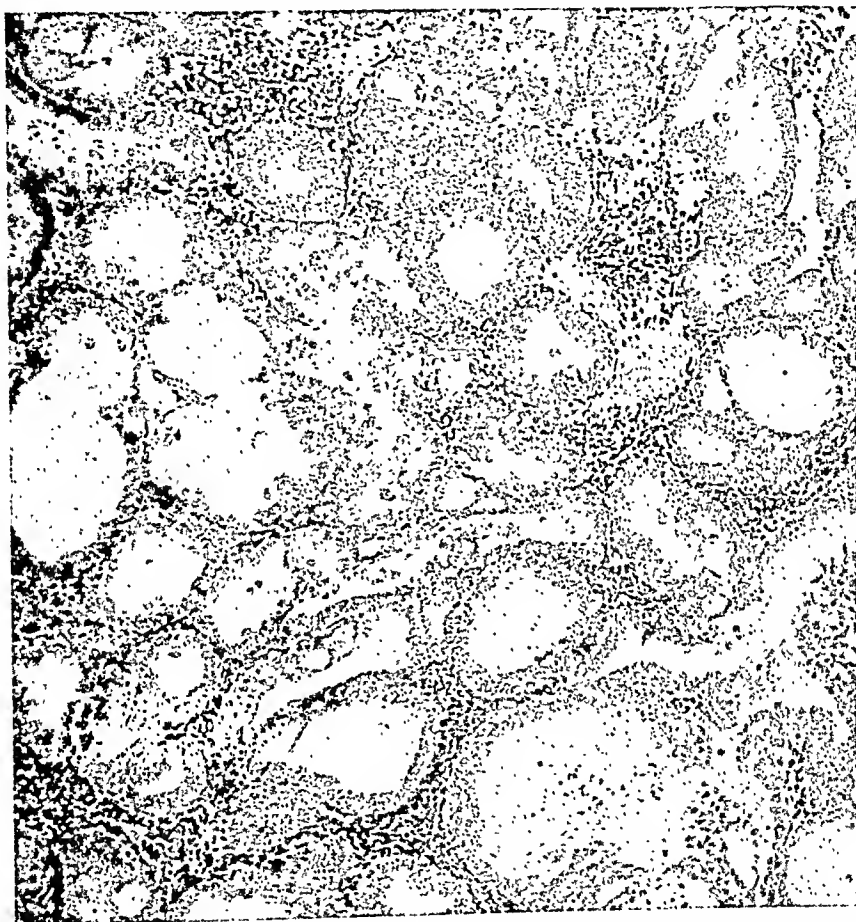


Fig. 7.—Endometrium of a postmenopausal patient after long-continued estrogenic therapy, showing adenocarcinoma.

A natural experiment in abnormal estrogen stimulation of the postmenopausal human uterus is set up in the patient who develops a granulosa-cell (or theca-cell) tumor of the ovary; hyperplasia of the endometrium is a common finding in this condition. It is interesting to note the increasing number of reports<sup>13-21</sup> which stress the relatively high incidence of corpus carcinoma associated with these tumors. This type of evidence is extremely suggestive of an estrogen-cancer relationship.

Another human experiment has been set up by the widespread administration of estrogens to postmenopausal women. We have studied 20 endometria with extreme degrees of hyperplasia produced by long-continued estrogen administration (Fig. 6). For the most part the medication used was stilbestrol,



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## Discussion

DR. W. A. COVENTRY, Duluth, Minn.—Climacteric or postmenopausal uterine bleeding can be due to too prolonged and continuous treatment with estrogenic substances, which produce an endometrial hyperplasia, as suggested by Taylor. This is becoming a common observation, especially when a curettage is performed for "spotting" in the 40 to 60 age group, and undoubtedly calls for a more rational approach to the administration of estrogenic substances.

The incidence of uterine bleeding at 40 years of age or over is certainly increasing markedly and, of course, has made it imperative to do more uterine curettements. However, I do not believe that there has been an increase in the incidence of malignancy of the fundus of the uterus. The consensus of most authors is that carcinoma of the fundus is far greater after the menopause than before, and that there is no correlation between the increased incidence of fibroids and the presence of malignancy; in fact, the combination of carcinoma and fibroids is quite rare.

In a review of 128 cases in Duluth over the past ten years, there were only three cases of carcinoma of the fundus of the uterus coexisting with fibroids, or an incidence of 2.9 per cent. Our pathologists report all of the cases of carcinoma of the fundus as Grade I (Broder's), which corresponds with the findings in the literature.

Opinions vary as to the proper treatment of these cases. From my experience, if there is continued spotting from the uterus, especially in a menopausal or postmenopausal patient, the correct treatment would seem to be a careful systematic curettage; if no malignancy is found in the tissue from the fundus, then I would de-estrogenize the patient by discontinuing estrogenic treatment. If, however, malignancy is found, I would give first a course of deep x-ray therapy, followed by a radical hysterectomy (removal of the entire uterus, plus the tubes and ovaries). In this way at least 99 per cent of the cases will be cured.

DR. CLYDE L. RANDALL, Buffalo, N. Y.: At the Buffalo General Hospital we have taken from the files the last 200 consecutive cases of cervical carcinomas and a like number of adenocarcinomas of the fundus and have charted the differences in their ages, weights, marital status, and parity.

Our observations substantiate those just reported by Dr. Corscaden, who noted that 24.8 per cent of his patients with carcinoma of the fundus and 5.6 per cent of women developing carcinoma of the cervix were single. Likewise we found that 18.7 per cent of our women with adenocarcinoma as compared with only 2.4 per cent of patients with cervical malignancy had never married. Similarly, Dr. Corscaden found 38.6 per cent of married women developing adenocarcinoma had no children, whereas only 16.6 per cent of women with carcinoma of the cervix had been nulliparous. We found that 28.2 per cent of married women developing adenocarcinoma had been childless, while only 13.9 per cent of patients with cervical carcinoma had no children. The number of children per parous individual was not reported by Dr. Corscaden, and we found no significant differences in that regard. The married women developing adenocarcinoma had borne an average of 1.66 children, whereas the women with carcinoma of the cervix had an average of 2.29 children.



endometrial hyperplasia, though he cannot label the curettings adenocarcinoma (Fig. 8). Similarly in the group of hyperplastic endometria produced by estrogens, there were none which one could call carcinoma, but there were some which produced such an uncomfortable suggestion of cancer in the minds of the experienced pathologists who studied them, that they advised removal of the uterus as a prophylactic measure.

All these suggestive bits of evidence have brought us to the belief that unopposed estrogenic stimulation, either endogenous or exogenous, may be one of the carcinogenic factors for the uterus if the genetic substrate is such as to create a properly cancer susceptible tissue. Whether the general constitution, the apparently unusual marital and childbearing experience can be connected with this evidence of estrogen activity is a matter for interesting speculation. The data are too meager for any definite conclusions, but are suggestive enough to stimulate further study along these lines.

### Conclusions

From these few observations it would appear that an unmarried woman and if married, childless, who was overweight and in comfortable circumstances is a likely candidate for a cancer of the corpus at some time in her life. If her menopause is characterized by excessive bleeding, the chances of her contracting carcinoma are still greater.

We have briefly mentioned several fragments of evidence suggesting abnormal estrogenic stimulation as one of the growth-stimulating factors.

The evidence presented suggests that women destined to have carcinoma of the corpus are measurably different from other women. More precise measurements of these differences should be made.

We wish gratefully to acknowledge the assistance of Dr. C. W. Dupertuis in the statistical analysis of these data.

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menopause, particularly a woman with clinical evidence of persisting estrogen effect in her postmenopausal years, should be regarded as predisposed to the development of adenocarcinoma in her uterus.

DR. EMIL NOVAK, Baltimore, Md.—Although we have long been in the habit of speaking of cervical inflammatory lesions as predisposing to the development of cervical cancer, there has been little said as to factors which might predispose toward carcinoma of the uterine body. Dr. Corscaden's remarks on the significance of an unusually late menopause are in line with the observations of Hobbes and Crossen, and my own experience makes me feel that this factor does have a significance. Another which he mentioned, and which he supported statistically in his recent paper on the subject, is that represented by a history of functional menopausal bleeding, since women who have been treated for such a disorder show a later incidence of carcinoma three and one-half times as great as others.

A third factor which has impressed me as of probable predisposing importance is the exposure of the postmenopausal endometrium to persistent estrogenic stimulation, in the absence of what may possibly be the protective influence of progesterone. That such postmenopausal production of estrogen occurs not infrequently is well known, and we have found postmenopausal endometrial hyperplasia not infrequently in association with adenocarcinoma. There would seem to be an obvious relationship between all three of the factors which have been mentioned.

The largest number of adenocarcinoma cases in Dr. Corscaden's cases were between the ages of 50 to 55 years, and a similar incidence is noted in studies by others. The significance of this, in relation to the factors previously mentioned, is tempered by the fact that mistakes in pathologic diagnosis are more frequent at this age period than at others, since at this time especially we are likely to encounter various degrees of proliferative or adenomatous hyperplasia which are easily mistaken for adenocarcinoma, although they are clinically benign. For example, several of the slides shown by Dr. Corscaden as instances of adenocarcinoma impress me as belonging to this pseudomalignant group, and not to be malignant.

The differentiation requires much pathologic experience, and in some cases must be made almost empirically by the trained microscopist. I have followed many of these cases clinically after conservative treatment, including curettage and radiotherapeutic induction of the menopause, and cancer has not developed. Furthermore, in a good many cases in which the uterus had been removed, further study showed no evidence of cancer. On the other hand, there is a small residue of cases, in which the doubt is very real, and in which pathologists will disagree, and in these the treatment should be that of carcinoma. From what has been said it is easy to understand how cancer statistics can be vitiated by the inclusion of cases in which the lesions are histologically pseudomalignant but really clinically benign.

DR. FRANK R. SMITH, New York, N. Y.—I would like to ask Dr. Corscaden whether, in this series of patients presented a preliminary curettage had been done before using stilbestrol. I think it is important that from these patients we should have at least a biopsy by Dr. Novak's method or by curettage before stilbestrol is administered to women of menopausal age.

I was interested that Dr. Corscaden noted 15 cases in 900 patients treated with irradiation that later developed carcinoma of the body of the uterus. During the years 1924 to 1934 at Memorial Hospital we had about 1,000 patients treated with small doses of radium for endocrine imbalance. Only four of that group have later developed carcinoma. We have had about 21 patients come to the hospital in later years who were treated at other hospitals during that period but who were not in this original group of 1,000. It is perfectly true that many of our patients might have developed carcinoma and gone to other hospitals. But in that case there is usually a letter requesting information which is filed with the record.

DR. ROBERT SEIBELS, Columbia, S. C.—My discussion will not be confined to the material presented. However, the promptness with which diagnosis and definitive treatment

I feel that the factors predisposing the individual woman to adenocarcinoma of the uterus must be recognized in her medical history and in the characteristics of her physique. It is important that we recognize the woman so predisposed, particularly if so-called routine pelvic examinations are to be employed as a cancer prevention measure. While local, visible changes may arouse our suspicion of cervical malignancy, little can be found on inspection or palpation to increase the examiner's suspicion of endometrial carcinoma. While carcinoma arising in the endometrium occurs less frequently than squamous-cell carcinoma of the cervix, the curability of fundal carcinoma assures it greater consideration than the mere frequency of the lesion would otherwise justify.

Granting the possible significance of certain characteristics of physique, I am personally convinced that endocrine dysfunctions associated with functional bleeding or a late menopause provide a practical basis for recognition of the woman predisposed to the development of adenocarcinoma of the uterus.

We have previously reported that over 35 per cent of women ultimately developing carcinoma of the fundus continued to menstruate past their fiftieth year. In comparison, among a group of women failing to develop uterine malignancy over a period of 15 post-menopausal years, 92 per cent had experienced cessation of their periods before their forty-ninth year. If the unopposed action of estrogen upon the endometrium results in an increased incidence of adenocarcinoma, it would seem logical to expect an increased incidence of this neoplasm within a group of women continuing to menstruate (and continuing their opportunity for ovarian dysfunction) several years longer than the average.

Occasionally we hear the suggestion that irradiation, when employed for the treatment of benign causes of bleeding, may bring about changes in the uterus that predispose that organ to the development of adenocarcinoma. The literature suggests that while the use of radium or x-ray may not prevent the subsequent development of endometrial malignancy, the postradiation changes in no way predispose the uterus to the development of adenocarcinoma. We, therefore, feel that a castration dose of irradiation is probably advisable whenever a diagnostic curettage is indicated for functional bleeding during the climacteric years. Moreover, when vaginal repair or a pelvic laparotomy is indicated for a woman past the childbearing age, in choosing the operative procedure it should be remembered that total hysterectomy would prevent the subsequent development of either cervical malignancy or adenocarcinoma in the fundus.

In the pathogenesis of endometrial carcinoma, an unopposed estrogen effect is not mandatory, for adenocarcinoma frequently develops before the menopause in the presence of a corpus luteum. There seems little evidence that the relatively transitory progesterone effect exerts either a positive or negative influence upon the development of adenocarcinoma in the uterus. On the other hand, as Dr. Corscaden has emphasized, evidence of prolonged estrogen stimulation occurs frequently in women developing adenocarcinoma of the uterus. Few believe that endometrial hyperplasia is a necessary precursor of adenocarcinoma, but the incidence of fundal carcinoma among women with a history suggesting prolonged estrogen effect and endometrial proliferation cannot be denied.

The development of endometrial malignancy in the uterus of a woman who has previously had both ovaries removed or who had been castrated by adequate doses of irradiation should not be offered as evidence that adenocarcinoma can develop in a uterus not previously primed by estrogen, *unless* the patient's vaginal membrane suggests the atrophic changes expected when estrogen deprivation persists over a period of time.

We have published statistics indicating that whenever postmenopausal bleeding occurs, the woman with a history of menorrhagia during her climacteric years has three and one-half times greater chance of having developed an adenocarcinoma of the fundus than does the woman who experienced no increased bleeding prior to cessation of her periods. It will be recalled that Dr. Corscaden's data substantiate that figure. I believe there is a fundamental principle evidenced in the observation that adenocarcinoma does *not* develop in the uterus while a woman is experiencing hot flushes, particularly if on examination she shows atrophic changes and no evidence of estrogen effect on the endometrial and vaginal membranes. Conversely, a woman experiencing functional menorrhagia or metrorrhagia at the

## PITUITARY EXTRACT IN UTERINE INERTIA: IS IT JUSTIFIABLE?\*

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THE procedures employed in the management of uterine inertia are, in the main, rather well standardized. In secondary inertia, the administration of morphine and intravenous fluids to provide a period of rest and promote hydration has proved widely satisfactory, and is usually followed in a few hours by a return of normal, effectual contractions. In primary uterine inertia, time and patience, repeated reassurance of the patient, and stimulation with enemas from time to time will likewise bring most cases to a happy conclusion. Occasionally, however, cases of primary uterine inertia may prove so refractory to treatment that the question arises as to the desirability of using a really effectual uterine stimulant such as pituitary extract; and ever since that agent was first introduced, some forty years ago, the problem of the justification of employing it in such cases keeps recurring.

The dangers of pituitary extract in the first and second stages of labor in the form of uterine rupture and fetal asphyxia have been repeatedly and vehemently emphasized and, in the opinion of many authorities, are so menacing that this agent should never be used before the birth of the baby. On the other hand, there is ample evidence that a real need for the oxytocic effects of pituitary extract exists if its action could be but safeguarded. Witness, for instance, the many efforts which have been made to moderate the effect of this hormone. Hofbauer's nasal pituitrin represented one such attempt, as did also thymophysin, the various preparations of pituitrin in oil and, more recently, Dieckmann's pitsulfonate. Within the past few months, moreover, Duncan Reid has reported some 1,500 cases from the Boston Lying-In Hospital in which small doses of regular pituitary extract or pitocin were used in the treatment of first- and second-stage uterine inertia with gratifying results.

Our own experience with pituitary extract in the treatment of uterine inertia began in 1926 with Hofbauer and Hoerner's introduction of nasal pituitrin. This was used extensively in our clinic for a ten-year period ending in 1935, but with results which were far from consistent. In some cases the effects were highly satisfactory, in others no action at all could be detected—depending apparently on the ability of the inferior turbinate bones to absorb the hormone. But we put up with these undependable results in the complacent belief that, in any event, it was safe. However, when in our own city, two cases were brought to our attention of ruptured uterus following intranasal pituitrin, we were rudely disillusioned about its safety and abandoned the procedure. Between 1935 and 1940, inclusive, no pituitary extract was employed before the

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are accomplished is bound to be reflected in the results achieved in the treatment of carcinoma either of the fundus or the cervix. I would like to review briefly the findings in a case of carcinoma of the cervix in which the diagnosis was primarily made from stained smears of the vaginal secretions. This 39-year-old patient came in for a routine physical examination presenting no symptoms suggestive of malignant change or, indeed, of ill health. The spread was made from vaginal secretions as a purely routine step comparable with the ordinary laboratory tests on urine and blood.

The photomicrographs shown tell the story. In the first one, there were areas of normal vaginal cells with an increase in the leucocytes. In the second is shown a single irregularly shaped cell with a tremendous nucleus.

In the third is shown a group of atypical basal type cells and another group of cells which are distinctly of cancerous appearance with irregularly shaped nuclei, taking stain in various densities and with a nuclear pattern quite typical of epidermoid carcinoma.

Based on these appearances, a biopsy was taken and the first cuttings from the block were compatible with the report of normal cervical tissue.

The next slide shows typical invasion of squamous malignant epithelium and on comparison with the stained smear we find exactly the same type of cells and cellular arrangement.

The sections from the operative specimen continued to show squamous-cell carcinoma of the cervix, Grade II. Here then is a case of early noninvasive carcinoma of the cervix primarily diagnosed by the stained smear and without its routine use it would have been completely overlooked.

DR. JAMES A. CORSCADEN, New York, N. Y. (Closing).—None of these patients in whom stilbestrol has produced a hyperplasia had received their stilbestrol from us. I do not believe that any of them had had a curettage. Apropos of the question of the merits of supravaginal and complete hysterectomy, 8 per cent of our cancer of the cervix lay in stumps following supravaginal hysterectomy. Four per cent is the figure given over the country in general. I believe that we should set an ideal and not teach that the best operation is one based on the capacity of the casual surgeon.

agent by less patient practitioners increases. This circumstance is certainly a heavy charge on the debit side of the pituitary ledger.

This series of private patients will appear again in our statistics when the dangers of pituitary extract are analyzed, and rightly so, because all these 230 women were exposed to its hazard. However, since most of them did not, in all probability, represent valid examples of uterine inertia, this group is of little help in answering the important question: what benefits may be expected from pituitary extract in true uterine inertia? For this purpose it is necessary to concentrate on our 233 ward cases, practically all of which were examples of real, often severe, inertia. We define uterine inertia as follows: in the first stage, sluggishness of uterine contractions (after true labor has begun) of such a degree that (1) the cervix shows no change over an eight-hour period, and (2) the uterine wall is easily indentable at the acme of each pain; in the second stage, sluggishness of uterine contractions of such a degree that the head neither rotates nor descends over a two-hour period with a uterine wall which is easily indentable at the acme of each pain. Uterine inertia and prolonged labor, let it be emphasized, are not synonymous, because prolonged labor may be entirely normal and physiologic, provided that steady, if slow, progress is made. Uterine inertia, on the other hand, is complete, prolonged absence of progress in the presence of weak contractions.

TABLE II. DURATION OF LABOR AND INCIDENCE OF INTRAPARTUM INFECTION IN PITUITRIN CASES, WARD AND PRIVATE

WARD CASES		PRIVATE CASES	
<i>Duration of Labor</i>			
Under 24 hours	108	Under 24 hours	206
25 to 30 hours	38	25 to 30 hours	12
31 to 47 hours	61	31 to 47 hours	9
48 hours and more	26	48 hours and more	3
	<hr/> 233		<hr/> 230
<i>Intrapartum Infection</i>			
Ward cases		Private cases	
58 or 24.9%		2 or 0.9%	

A good idea of the general character of these 233 ward cases in which pituitary extract was used may be had from Table II, where it may be seen that over half the labors exceeded twenty-four hours, and in one-fourth were associated with intrapartum infection. In 87 cases, or 37 per cent, the duration of labor exceeded thirty hours, and in 26, or 11 per cent, extended over more than forty-eight hours. As a rule, pituitrin was not started until eighteen to twenty-four hours of labor had elapsed with weak pains and a stationary cervix, and after, of course, all the usual expedients, such as enemas, had proved ineffectual. Indeed, the problem of whether or not to use pituitrin in these cases was not so much one of pituitrin vs. further temporizing as it was that of pituitrin vs. some radical method of delivery; and I can give you no more concrete picture of the type of case in which we have used pituitrin on the ward service than by saying that we have employed it, in the main, in the patient who seems to us to be headed, in the next day or two, either for Dührssen's incisions and a difficult midforceps, or extraperitoneal cesarean section.

birth of the baby. During these five years, we repeatedly felt the need for a reliable uterine stimulant, especially in the first stage inertia, and were particularly disturbed by one maternal death in which uterine inertia played a major role—a case in which prolonged, stubborn inertia, exhaustion, intra-partum infection, Dührssen's incisions, and a difficult midforceps produced a fatal degree of shock. And we can recall a few similar cases of extreme inertia in that period in which the mother did not pay the death toll, but escaped only by a narrow margin.

Being impressed, therefore, not only by the frequency of primary uterine inertia, but by its grave potentialities, we began on Jan. 1, 1941, to treat carefully selected cases of uterine inertia with minute, intramuscular doses of pituitary extract. During the first two years of the program, the initial dosage was limited to 1 minim, during the last three years to  $\frac{1}{2}$  minim. Injections are repeated every thirty minutes until satisfactory pains ensue. If no effect whatsoever on the quality of the contractions is observed, the dose may be increased, but this was never allowed to exceed 2 minims. Recently, the upper limit for a single dose has been reduced to 1 minim. The number of injections ranged from one to as many as 35 in a few cases; the average was perhaps three or four. In the great majority of the cases this therapy was carried out in the first stage of labor. Further details of this experience will be published shortly by Dr. Louis M. Hellman of our Department in a more comprehensive study than can be presented in the time limit for this paper.

TABLE I. INCIDENCE OF PITUITRIN STIMULATION, 1941 TO 1945

	CASES	PITUITRIN	PER CENT
Total	8679	463	5.3
Ward patients	6680	233	3.5
Private patients	1999	230	11.5

As may be seen in Table I, pituitary extract was used in 463 cases with an over-all incidence of 5.3 per cent. When our total cases, however, are divided into ward and private patient groups, a glaring discrepancy appears, namely, a three times greater incidence of pituitrin stimulation in private patients than in our ward clientele. This means only one thing, namely, that some of our visiting obstetricians are employing pituitary extract not infrequently for very minor degrees of uterine inertia—cases which patience and time would probably have brought to a satisfactory outcome without oxytocic stimulation. Although there was not a single fetal death in the 230 private cases (except for a fetal monster carried several weeks dead in utero), this practice of employing pituitary extract in virtually normal labor is reprehensible. At the very outset of our study, then, we are confronted with one of the great drawbacks to countenancing any use of this agent before the birth of the baby, namely, its inevitable abuse. Certainly, our experience, as shown in Table I, would indicate that just as soon as any group of obstetric specialists in a community begin to employ pituitary extract before the birth of the baby—be they ever so careful to restrict its use to rigorously selected cases of true inertia—the unnecessary administration of this

babies were alive on admission, the infant loss, from both stillbirths and neonatal deaths, was 3.0 per cent. We consider this a creditable figure. All these 14 deaths occurred in the 225 ward cases, giving a mortality rate of 6.2 per cent for this group. When it is recalled, however, that 58, or one-fourth, of these ward patients suffered from intrapartum infection, and over one-half had labors exceeding twenty-four hours, it seems doubtful if this figure could be greatly improved upon except by wholesale cesarean section. Certainly it would have been much higher had many midforceps been employed in these cases instead of pituitrin stimulation.

TABLE V. CAUSES OF 14 FETAL DEATHS IN PITUITRIN SERIES

CAUSE	CASES
Pituitrin (5 cases of unrecognized or disregarded, borderline disproportion)	8
Maternal rupture of uterus (pituitrin)	1
Forceps trauma	2
Difficult breech extraction—4,340 Gm. infant	1
Encephalocele	1
Maternal eclampsia, prematurity (mother died)	1
	14

The causes of the 14 infant deaths are listed in Table V. Nine of them appeared to be the direct result of pituitrin stimulation. In one, fetal exitus followed rupture of the uterus—a case which will be presented in detail presently. In the other eight, the fetal heart sounds disappeared in the course of the administration of the hormone. It is instructive, from several points of view, to note that in five of these eight cases, unrecognized or disregarded, borderline disproportion was present. In two cases subsequent x-ray pelvimetry showed mid-pelvic contraction, which had been overlooked clinically. In another, the infant weighed 4,520 grams. In two, although the diagonal conjugates were borderline—11.5 cm.—it was thought that the heads had passed the superior straits and, since both patients had intrapartum infection, it was decided that the cautious administration of  $\frac{1}{2}$  minim doses of pituitrin was preferable to extra-peritoneal cesarean section. These cases emphasize clearly the high fetal mortality which may be expected if pituitrin stimulation is used in the presence of the slightest degree of disproportion. It may well be argued that this fact itself is an insuperable objection to the use of pituitrin stimulation since, even if one exercises meticulous care and possesses uncanny judgment, a case of borderline disproportion may now and then be overlooked. It is for this reason that we strongly favor x-ray pelvimetry prior to pituitrin stimulation.

There was one maternal death in the pituitrin series in no way associated with the use of the oxytocic. The patient was an eclamptic to whom a single  $\frac{1}{2}$  minim dose of pitocin was administered early in a lagging labor; she died post partum of eclampsia.

There was one case of uterine rupture as follows: The patient was a 44-year-old white woman, para viii, weighing 200 pounds, with a pelvis shown to be ample by x-ray pelvimetry. The fetus was in vertex position, with the head at the spines, and was thought to weigh about 4,000 grams. After twelve hours of



Having defined uterine inertia, as we regard the term, let us consider what benefits, if any, have accrued during the five-year period in which pituitary extract has been used in the treatment of this condition, as compared with our experience over the preceding five-year period when it was not employed. This is summarized in Table III. It will be noted that there was no diminution in prolonged labor; and from what has been said, this was not to be expected. The majority of these prolonged labors were considered normal, if slow, and pituitary extract was therefore not administered.

TABLE III. BENEFICIAL EFFECTS OF PITUITRIN STIMULATION, WARD CASES ONLY

	PERIOD 1936-40	PERIOD 1941-45
Total deliveries	5529	6680
Pituitrin stimulation	0	233 (3.5%)
Prolonged labor		
Over 24 hours	456 (8.2%)	564 (8.4%)
Over 30 hours	265 (4.8%)	329 (4.9%)
Midforceps	26	6
	(1:212 deliveries)	(1:1113 deliveries)
Dührssen's incisions	10	5
	(1:553 deliveries)	(1:1360 deliveries)
Total cesarean sections	287	254
	(5.2% or 1:19 deliveries)	(3.8% or 1:27 deliveries)
Cesarean section after pituitrin	--	8
		(3.4% or 1:29 deliveries)

Perhaps the most notable benefit which we have derived from the use of pituitrin is the dramatic reduction in the incidence of midforceps, from 1 in every 200 deliveries in the nonpituitrin period to 1 in every 1,000 in the pituitrin period. We believe this represents an important saving in fetal life and maternal trauma. The same is likewise true of the 50 per cent reduction in the frequency of Dührssen's incisions. The diminution in the frequency of cesarean section was doubtless the result of many factors, but we feel certain that the use of pituitrin as we have described it played an important role in the lowered incidence. Substantiation is given to this statement by the fact that in this entire series of 233 functionally pathologic labors, only eight cesarean sections were done, that is, in 3.4 per cent of the cases. Had it not been for pituitrin, I am certain that the number of abdominal deliveries would have been several times this figure. Of the eight cesarean sections performed, four were Water's extra-peritoneal operations, two were cesarean section-hysterectomies, and two were lower cervical sections with prophylactic penicillin and sulfadiazine.

As shown in Table IV, the uncorrected fetal mortality in the total series, ward and private, was 5.0 per cent. Nine of these 463 patients, however, had suffered fetal death in utero before admission to the hospital, and, if these be excluded from the present analysis, it will be seen that among the patients whose

TABLE IV. FETAL MORTALITY IN PITUITRIN SERIES

	CASES	DEATHS	PER CENT
Total (uncorrected, stillbirths and neonatal deaths)	463	23	5.0
<i>Fetus Alive on Admission</i>			
Total	454	14	3.0
Ward	225	14	6.2
Private	229	0	0.0

in obstetrics is to try to "push" labor in patients who are not in labor at all; pituitary extract will only lead to trouble in such cases.

3. There must be no mechanical obstruction to easy delivery as attested by every type of evidence possible, including x-ray study of the pelvis and fetal skull. Unless the latter is done, an occasional instance of midpelvic contraction or of brow presentation may be overlooked.

4. Patients of great parity (paras iv and over, let us say) must not be given pituitary extract because their uteri rupture more readily than those of women in the lower parity brackets.

5. The condition of the fetus must be good, as evidenced by a regular heart beat and absence of meconium-stained liquor amnii. A dead fetus is, of course, no contraindication to pituitary extract.

6. The obstetrician must observe and time the first contraction after the administration of the drug, and given inhalations of ether if it lasts longer than three minutes.

7. *The initial dose must not exceed 1/2 minim.* This dosage should not be exceeded unless it is clear that no improvement in pains whatsoever ensues. In the latter event, it may then be increased to 1 minim, but under no circumstances should more than 1 minim be given at a time. A period of thirty minutes must intervene between injections.

8. When in doubt as to whether a given case meets the above criteria, do not give pituitary extract.

### Discussion

DR. TIFFANY J. WILLIAMS, Charlottesville, Va.—Dr. Eastman makes a distinction between uterine inertia and prolonged labor, but it seems to us that prolonged labor in the absence of obstruction or obvious cervical abnormality is usually associated with varying degrees of uterine inertia. The management of individuals with inertia taxes the ability and patience of the obstetrician, and judicious attempts to stimulate rhythmic uterine contractions are justifiable.

Dr. Eastman does not distinguish in his cases between those with intact and those with ruptured membranes. In those in whom the membranes are intact contractions frequently may be stimulated by artificial rupture of the membranes, and what was formerly an ineffective labor may progress rather promptly to a satisfactory conclusion. If inertia is present after rupture of the membranes, the difficulties are more profound. In instances of inertia, as indeed in all parturient patients, the attendant must assure himself by all available methods of examination including anteroposterior and lateral x-ray measurement films of the pelvis, that no pathologic condition which might interfere with the mechanism of labor exists. Only under those conditions, and with the presenting part well engaged in the pelvis, should one consider the administration of pituitary extracts. The use of pituitrin to stimulate uterine contractions is often a gratifying procedure, but one which is fraught with dangers. We doubt that it should be administered to a patient who is having uterine contractions. The patient to whom it is being administered should be under the constant observation of the physician, and some form of general anesthesia must be immediately available. We personally prefer the intranasal administration, which necessitates the physician's constant presence, so that he can promptly evaluate the uterine response. Under these conditions the chances of prolonged tetanic contraction with rupture are quite remote.

The outlook for patients with uterine inertia and prolonged labor has been appreciably improved in recent years with the present methods of chemotherapy and supportive

labor, the last ten of which were characterized by poor pains and a cervix stationary at 3 cm., a series of nine injections of pituitary extract were given thirty minutes apart, the first three being 1 minim and the last six, 2 minims. Shortly after the last dose was administered, signs of rupture of the uterus developed, and this diagnosis was confirmed at laparotomy, a large rent being present on the left side of the uterus. The 4,250 Gm. child was dead, but the mother made a satisfactory convalescence after hysterectomy.

The case is reported with due humility and with full awareness of our heavy culpability. Although nothing can be said to extenuate this accident, it should be observed that it occurred during the first year of our use of intramuscular pituitrin stimulation, and that today we would not think of giving such a patient this form of medication because she presented one of the most important contraindications to pituitrin stimulation, namely, great multiparity. Evidence of various types shows conclusively that uteri which have carried five or more babies rupture, from all causes, much more readily than the primigravidous uterus, which is relatively immune to this accident.

In addition to this definite instance of uterine rupture, there was one suspected case in which the patient developed a tender mass to the right of the uterus twenty-four hours post partum. Whether this represented a slight rupture or parametritis was uncertain.

Here, then, are the main data on our experience with pituitrin stimulation. Some of you may conclude that the results, particularly the outright case of uterine rupture, should outlaw its use. Others may feel that the benefits achieved outweigh the drawbacks. My own reaction is stated in the following conclusions.

### Conclusions

Even if all precautions are exercised, pituitary extract, when given in the first or second stages of labor, will occasionally cause the death of an infant and, less frequently, may result in rupture of a uterus; hence, it is a dangerous drug when given before the birth of the baby. But, looking at the other side of the ledger, uterine inertia also takes its toll in terms of intrapartum infection, exhaustion, difficult forceps, Dührssen's incisions, etc. Which is the lesser evil: pituitary extract or stubborn uterine inertia? Having been brought up to believe that the administration of pituitary extract before the birth of the baby constitutes the most heinous of obstetric sins, but during the past five years having observed its ultra-cautious use in several hundred cases of uterine inertia, I am inclined to believe that the balance lies slightly in favor of pituitary extract—provided, and provided again, that certain rigid rules be observed, as follows:

1. The case must be one of real uterine inertia, primary in character, with labor practically at a standstill and progress nil.

2. The patient must be actually in labor, not in false or prodromal labor. The only valid evidence of true labor is progressive effacement and dilatation of the cervix. Although this process may have come to a standstill, it must have progressed to the extent of 3 or 4 cm. dilatation. One of the commonest mistakes

I used the nasal method of giving pituitary extract as advised by Dr. Hofbauer for many years, but I am now using the hypodermic technique which Dr. Eastman has just described. I have never seen a serious case of tetanic contraction of the uterus when the drug is used with care, and I believe firmly that its administration is a distinct help in uterine inertia. I think that uterine inertia is one of the most serious delivery room problems that we have to face and that anything that promises benefit safely should be used to combat it. I agree with Dr. Williams that rupture of the membranes will often help and, of course, the patient should be given as much rest and nutritive fluid as possible. I have never used Dührssen's incisions, but prefer to dilate the cervix manually when it is necessary to do so.

DR. JAMES R. BLOSS, Huntington, W. Va.—I wrote a paper, published more than twenty-five years ago, on "Pituitrin versus Forceps." I was all for pituitrin. I want to agree with Dr. Eastman that the use of pituitrin in carefully selected cases of uterine inertia is not a particularly dangerous procedure. Its use in certain cases, ruling out obstructions, deformities of the pelvis, disproportion, and so on, is often very helpful. With minimum doses, repeated as the effect wears off, proper contractions follow. I believe that you get a synchronization of the uterine contractions without a physiologically explosive effort in cases which are carefully chosen. I did home obstetrics for many years and used much pituitrin. I have never seen a ruptured uterus following its use. I have noted some contraction rings. Five minims of adrenalin hypodermically will relieve contraction ring in a very few moments. Also the careful and intelligent use of chloroform will stop these tetanic contractions from pituitrin almost instantly.

I agree thoroughly that there should be an adequately trained obstetrician. Some persons may have five or ten years' training, some may do obstetrics over a period of twenty years, and yet not have judgment enough to use anything intelligently. I second Dr. Eastman's plea for the judicious use of pituitrin in carefully selected cases.

DR. R. L. DENORMANDIE, Boston, Mass.—I find myself in almost complete agreement with Dr. Eastman. I have never failed to use pituitrin in carefully selected cases, never starting with more than one minim. I never give another unless I have an anesthesiologist near by to give ether should the patient's uterus go into tetanic contractions. I stopped using it for a while because of the tetanic contractions, but have come back to its use.

I do not hesitate to use it in multiparas of the type that Dr. Eastman refers to, provided I know by previous examination that there is not a cicatrix in the cervix or a bad bilateral tear.

DR. J. BAY JACOBS, Washington, D. C.—This paper seems to center around pituitrin, and the emphasis seems to be on pituitrin rather than on primary or secondary inertia. I am in accord with the essayist and the discussants relative to the dangers of pituitrin, but I believe we have overlooked one important factor in the treatment of inertia, and that is rest. Very often a tired woman needs rest and then her uterine contractions will be of a good character. We must differentiate also in cases of inertia, as to whether it is primary or secondary. In primary inertia uterine contractions may not be very forceful, but quite regular; even though the cervix is not dilating, the woman appears to be in labor. If the cervix seems to be rigid, or "non-negotiable," as Potter says, I would administer a hypo of dilaudid gr.  $\frac{1}{32}$  and scopolamine gr.  $\frac{1}{200}$  and probably stop the labor, rather than encourage it. On the other hand, if it appears that some progress has been made and the patient is not tired, I might consider rupturing the membranes. If progressive labor did not ensue, I would proceed with small doses of pituitrin as outlined by Dr. Eastman, and if response were then slow, would also order an enema.

Secondary inertia implies that after a certain amount of progress had been made resulting from a normal type labor, retardation occurs due to ineffective uterine contractions. If the patient is not tired, rupture of the membranes will usually re-establish an effective labor. If the response should be slow, a hot enema and a small dose of pituitrin

treatment. Intravenous glucose with vitamins combats exhaustion and dehydration, and penicillin prophylactically during labor and after rupture of the membranes reduces the frequency and severity of intrauterine infection, and seems to appreciably enhance the chances for survival of the infant.

The necessity for the employment of Dührssen's incisions is really quite frequent, and their use is more often an indication of exhaustion of the attendant rather than exhaustion of the patient. Indeed, rarely if ever is the welfare of the mother or baby enhanced by vigorous and traumatic operative procedures. Usually the prolongation of the labor is safer than its termination by violent vaginal operations. We have employed Dührssen's incisions in our clinic only twice in the past fifteen years.

Dr. Eastman's point regarding the danger of rupture of the uterus in the "*grande*" multipara is well taken and we agree that the use of pituitrin in these individuals is associated with an excessive hazard.

Doubtless, if the course and duration of labor in uterine inertia could be predicted at the onset, many of us would advise abdominal delivery, rather than pursue the slow and tedious course required for vaginal delivery. Murphy has suggested that, by means of the Lorand tocograph, primary uterine inertia may be detected early in labor. It is conceivable that future studies of recordings of uterine tone and contractions may develop to the point where they will significantly affect our decision regarding the method of delivery sufficiently early in labor to safely perform a cesarean section.

I should like to ask Dr. Eastman if he can tell us what is the frequency of inertia in the same patient in subsequent labors? Will subsequent labors also be characterized by inertia? Many times both the patients and ourselves have been too timid to face subsequent labor with its possibility of another inertia and instead we have delivered them by elective section. I have often wondered whether this has been a justifiable decision.

DR. JAMES K. QUIGLEY, Rochester, N. Y.—About 1915, I read one of the earliest papers on the use of pituitary extract in obstetrics. Before ten years had passed I began to regret the publication of that paper, which regret was prompted by several things. The first was the necessity of removing two badly ruptured uteri in a ward service, and I have seen contraction ring dystocia in some cases of my own. I cannot tell you how long ago I abandoned the use of pituitrin before the birth of the baby, but it must be at least fifteen years. In the paper which I read at that time I talked of several precautions that should be observed in the use of pituitary extract during labor, such as full dilatation of the cervix and engagement of the head. Pituitary extract may be used with safety and I have no doubt that Dr. Eastman can use it with safety, but my point today is that I think it is bad teaching, a bad example to have go out from this organization. We have spent years in discouraging the use of pituitrin and we now rarely see it given, even by the general practitioner in our part of the country, and I am aware that after this paper we may encounter some ill effects that follow its use.

DR. GEORGE M. SHIPTON, Pittsfield, Mass.—As Dr. Quigley has said, we have been through a wave of administering pituitrin and are back out of it. I would like to add to Dr. Eastman's remarks a word of explanation. I think this paper is a sort of rebuttal to the recent papers which have been coming out urging the use of pituitrin. Dr. Eastman very carefully analyzed the cases and concluded by saying that in his own experience constantly throughout this experiment the dose of pituitrin had been reduced until it was down to a half minim, and then said, "If there is any doubt, let's not use it." The point of his remarks seemed to be simply to warn us again to get away from the use of pituitrin.

DR. JOHN M. BERGLAND, Baltimore, Md.—I agree with everything Dr. Eastman has said. I was obstetrically brought up by the late Dr. Whitridge Williams in the days before pituitary extract was used. We, of course, used ergot but with very definite rules for the administration of the same. Never until after the delivery of the baby and placenta was it given.

# AN ANALYSIS OF DEATHS FROM POSTPARTUM HEMORRHAGE\*

CLAYTON T. BEECHAM, M.D., PHILADELPHIA, PA.

*(From the Maternal Welfare Committee of the Philadelphia County Medical Society)*

**D**URING the fifteen years 1931 to 1945 inclusive, there were 520,489 deliveries in Philadelphia. Over this fifteen-year period there were 1,987 maternal deaths, for an average of 38.17 in every 10,000 deliveries, i.e., live and stillbirths. We wish to point out that in this study all figures (both for the United States and Philadelphia) are based on total births. It is customary to express mortality figures in the "number of deaths per 10,000 live births." Following that line of analysis we would exclude from this study many women who perished along with their babies in obstetrically preventable deaths. For this reason we believe that an analysis of postpartum hemorrhage deaths per live births does not give a true picture of obstetric events (Fig. 1).

This also shows the annual deliveries, the maternal mortality, and mortality from postpartum hemorrhage over the fifteen years under discussion. The top line illustrates the influence of economic conditions and war on birth rate. The second line in the graph illustrates the maternal mortality in Philadelphia. Here we start with the disgraceful figure of 248 deaths, or 70.28 in every 10,000 deliveries, for the year 1931. More significant, this date marks the beginning of the activities of the Maternal Welfare Committee of the Philadelphia County Medical Society under the able leadership of Philip F. Williams. The consistent downward trend of this second line in spite of an increased birth rate during the past six years proves the value of this committee's work. In 1945 there were 81 deaths in 39,956 births, or 20.27 per 10,000, for a reduction in maternal mortality of 50.01 per 10,000 deliveries in fifteen years.

In Fig. 2 we have shown the mortality rate for the United States during the years 1931 to 1943 inclusive, along with the rate for Philadelphia. Except for three years, the Philadelphia figures were an improvement over those for the nation. Notwithstanding, there remains one set of mortality figures at a constant level over the years—those for postpartum hemorrhage. To amplify the small but constant group of cases shown in Fig. 1, we have enlarged the picture in Fig. 3. This represents 168 deaths from postpartum hemorrhage or 8.45 per cent of the total in fifteen years. The average is 11.2 deaths from this cause a year. The sharp rise in the year 1932 was due to Philadelphia's one excursion into the realm of manual dilatation of the cervix and version.

Though the deaths from postpartum hemorrhage remain small and constant in number, the Maternal Welfare Committee has judged 121, or 72 per cent, of these deaths to be preventable (Table I). One hundred five or 62.5 per cent were judged preventable deaths due either to errors in judgment or technique on the part of the attending obstetrician. The patient either through carelessness or ignorance was held responsible for her own death in 9.5 per cent of the cases.

## General Considerations

Home deliveries have gradually declined throughout the country over this fifteen-year period, and this is also true for Philadelphia. Of the deaths from postpartum hemorrhage, 21 patients were delivered and died at home, while four were delivered at home and died in a hospital.

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

by hypo will usually accomplish desirable results. If it is evident that the patient and uterus are tired, she should be given several hours of rest, followed by appropriate stimulation such as enema, small dose of pituitrin, or rupture of membranes, depending upon the degree of stimulation that seems appropriate.

I believe there is danger in the repeated use of pituitrin over a long period of time. One case of Dr. Eastman was given nine injections of small doses at 30-minute intervals. Perhaps that was not a factor in causing rupture of the uterus in that particular case. However, I do believe that if one tries to stimulate a tired uterus hour after hour, the condition becomes aggravated. Frequently, the patient and her uterus need a good rest, followed by the procedure previously described. It is inadvisable to whip or push a tired uterus. The importance of rest should not be overlooked.

DR. HAROLD L. GAINNEY, Kansas City, Mo.—I disagree with those who think that this paper might have a deleterious effect on the general man. My reason for not giving pituitrin in these prolonged labors is not the disproportion between the fetus and cervix, but due to a cervix which is not ready to dilate, and perhaps these poor contractions are a physiologic response to a cervix not prepared for labor. I would be very much interested in knowing if Dr. Eastman has noted that particular difference in the cervix of a patient in prolonged labor, and rather than to concentrate on inertia and disproportion, is it not a safe physiologic response to a cervix that is not physiologically at term and ready for dilatation? I have seen a case where the contractions became so severe that we had to relieve the intensity of the contractions both for the safety of the mother and the baby.

DR. M. PIERCE RUCKER, Richmond, Va.—How do you differentiate the constriction ring always from the simple inertia?

DR. EASTMAN (Closing).—Dr. Williams has made some very astute and practical comments. Artificial rupture of the membranes is a most valuable procedure. I do not have the exact figures with me, but somewhere between 85 and 90 per cent of the patients in the series reported had ruptured their membranes spontaneously prior to the use of pituitrin. Of course, the management of uterine inertia is made much safer today by the use of penicillin and sulfonamides.

I would answer Dr. Williams' question in the negative, that is: uterine inertia does not tend to repeat.

The question was brought up by Dr. Jacobs and several others as to whether we were doing the right thing in condoning in any way the use of pituitary extract, because it would be a bad teaching principle to go out from this Association. Dr. Quigley says that in Rochester the doctors are not using pituitary extract. That does not hold true in Maryland, and I have a feeling that general practitioners throughout the country, despite all the emphasis on the dangers of it, are employing it and in large doses, and I do not think we should be so naïve as to think that any statement from this Association is going to have much effect on those men. They have tried it and achieved good results most of the time, and will continue with its use. It is my feeling that emphasis on contraindications and small dosage might do more good than the recommendation to eliminate its employment entirely.

I am very much perplexed as to how to answer Dr. Rucker's question about constriction rings. I know of his experience and I read with great interest Dr. Herman Johnson's paper stating that he had one constriction ring in every 80 labors. We must miss a great many of these constriction rings because we do not see them with such frequency as that, but it may be that many of our uterine inertia cases might be called by others constriction rings. We see what we say is a constriction ring once or twice a year, and even then are inclined to put a question mark after the diagnosis.

Dr. Gainney asked about the cervix. Many of these patients with prolonged labors have unfavorable cervixes, but what can be done about it? The condition is part of the picture.

TABLE I. DEATHS FROM POSTPARTUM HEMORRHAGE

Preventable by the Doctor	105— 62.5%
Preventable by the Patient	16— 9.5%
Nonpreventable	47— 28.0%
Total	168—100.0%

The ages of the women dying of postpartum hemorrhage ranged from 15 to 44 years, with an average of 31.5 years. The group was predominantly white, 84 per cent, against 16 per cent Negro. These women averaged four pregnancies apiece, and had three living children. The largest number of pregnancies in any patient was 17.

Labor began spontaneously and membranes ruptured spontaneously in the average case. The longest recorded labor was one hundred fifty-eight hours, but the group averaged fourteen hours. In the vast majority of cases one was not impressed with long labor as being an etiologic factor in the development of postpartum hemorrhage.

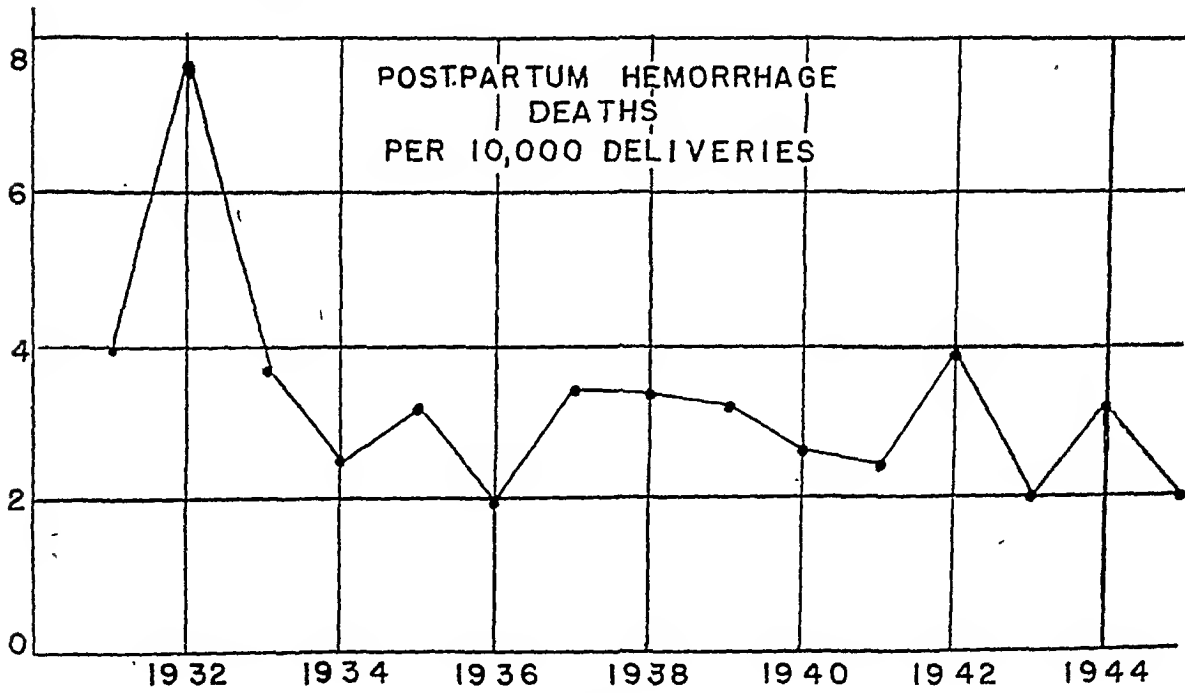


Fig. 3.

It was hoped that information on analgesic agents used might prove fruitful in our search for causative factors. The records in this regard were most incomplete. Twenty patients received barbiturates, usually in small doses, 15 women were given morphine and scopolamine. Sixty-three women received none, while 70 charts carried no information regarding this point.

Type of Delivery

Fig. 4 illustrates the percentage distribution of various methods of delivery used in the 168 women. There were five sets of twins in the group. One-third of the patients delivered spontaneously, while the remaining two-thirds had various obstetric operations. The committee felt that some of the operations were indicated, but the vast majority were not. Manual dilatation of the cervix and version was uniformly condemned. This operation reached



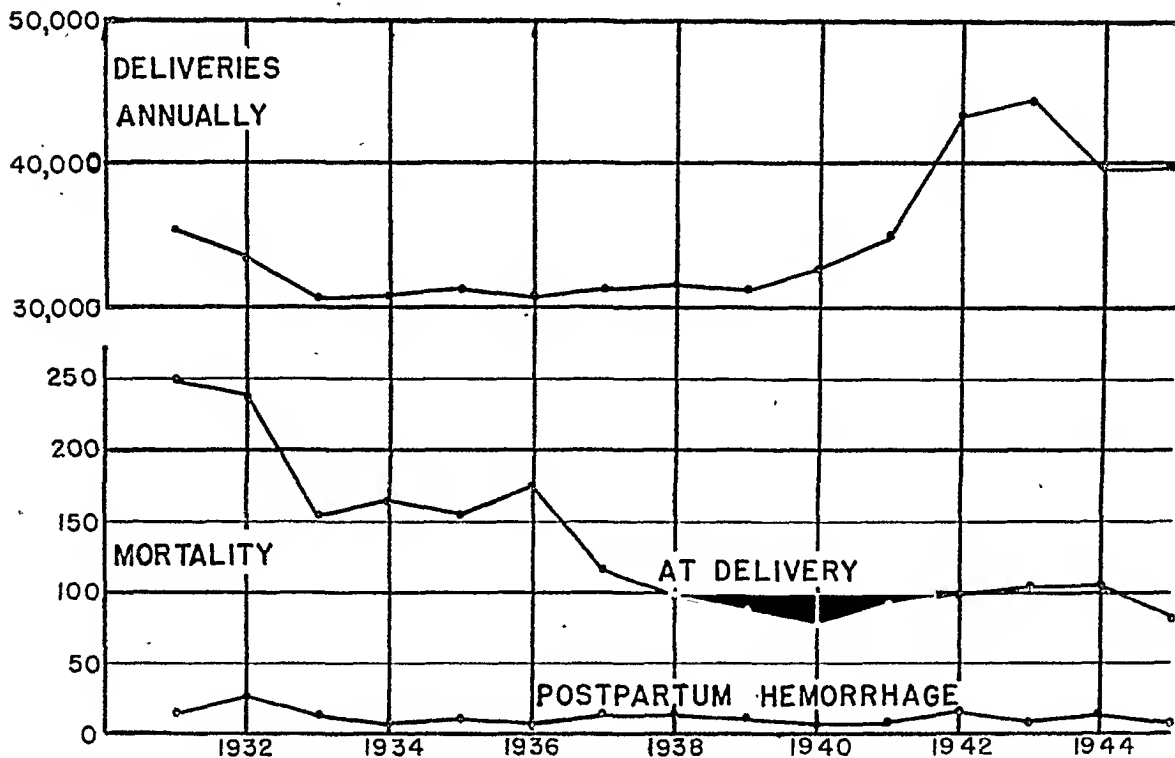


Fig. 1.

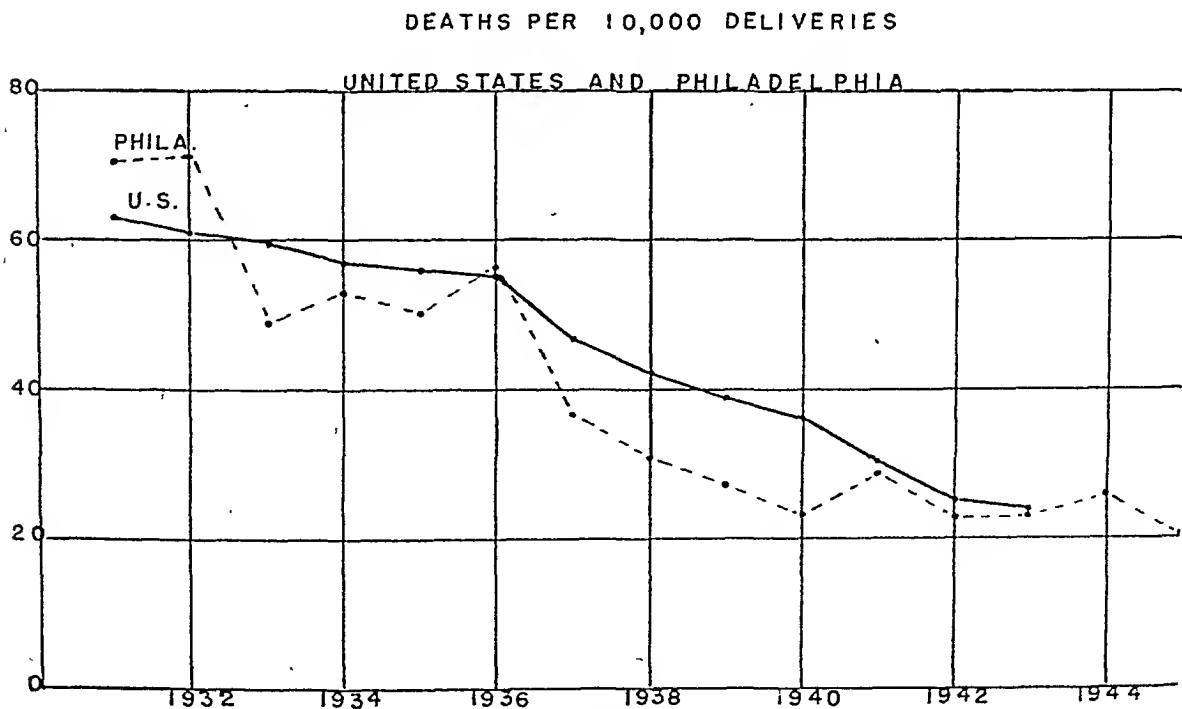


Fig. 2.

anesthesia are missing from the list brings up an interesting point. We know these agents have been increasingly used in Philadelphia. One could maintain that the very absence of regional anesthesia from the list proves that it is the method of choice as a safeguard against postpartum hemorrhage.

Here we are faced with the old saying that anything can be proved by figures. I feel that these data are inconclusive and must be re-evaluated after another time interval, when regional anesthesia is as widely used as general anesthesia.

### The Third Stage of Labor

One-third of the patients were given a pituitary solution at the beginning of the third stage of labor, and some ergot preparation at the completion of placental delivery. The remainder had oxytocies used only at the end of the third stage (Fig. 6).

Where inhalation anesthesia was used for delivery it was continued, in spite of abnormal bleeding in many cases, until the placenta was delivered. Suprafundal pressure was sufficient to express two-thirds of the placentas in the group, and 12½ per cent were removed at cesarean section. The remainder offered complications and were dealt with as outlined in Fig. 6. Manual removal of the placenta was done when the bleeding was excessive, and the third stage could not be completed otherwise. Late manual removal was done after a long period of bleeding and the patient was in deep shock.

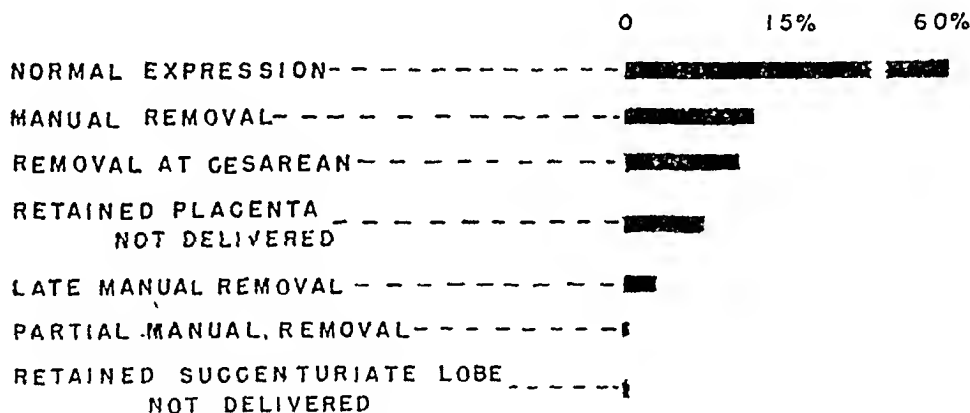


Fig. 6.—Placental management; percentage management.

TABLE II. ETIOLOGY OF POSTPARTUM HEMORRHAGE

ETIOLOGY	NUMBER	PER CENT
Atonic uterus	75	44.64
Atonic uterus following placenta previa	25	18.89
Atonic uterus following abruptio placenta	15	8.92
Atonic uterus following twins	5	2.97
Atonic uterus following hydramnios	1	0.59
Retained placenta—not delivered	12	7.15
Inversion of the uterus	11	6.54
Ruptured uterus	7	4.16
Lacerated cervix	7	4.16
Myoma uteri	4	2.38
Lacerated cervix and lower uterine segment	1	0.59
Lacerated upper vagina	1	0.59
Bleeding uterine incision	1	0.59
Bicornate uterus	1	0.59
Retained succenturiate lobe	1	0.59
Retained cotyledons	1	0.59

its highest popularity in 1932. Since then its frequency in fatal cases has gradually declined. The Maternal Welfare Committee justly takes credit for this awakening by holding open and free discussion on all these cases. No one could fail to be impressed by the difficulties encountered by extremely skillful operators. It was in this group of cases where a very high incidence of stillbirths occurred.

As a factor in the etiology of postpartum hemorrhage, operative obstetric procedures must receive first line attention. Complications ran higher where interference was practiced, although the spontaneous delivery group was not free of complications.

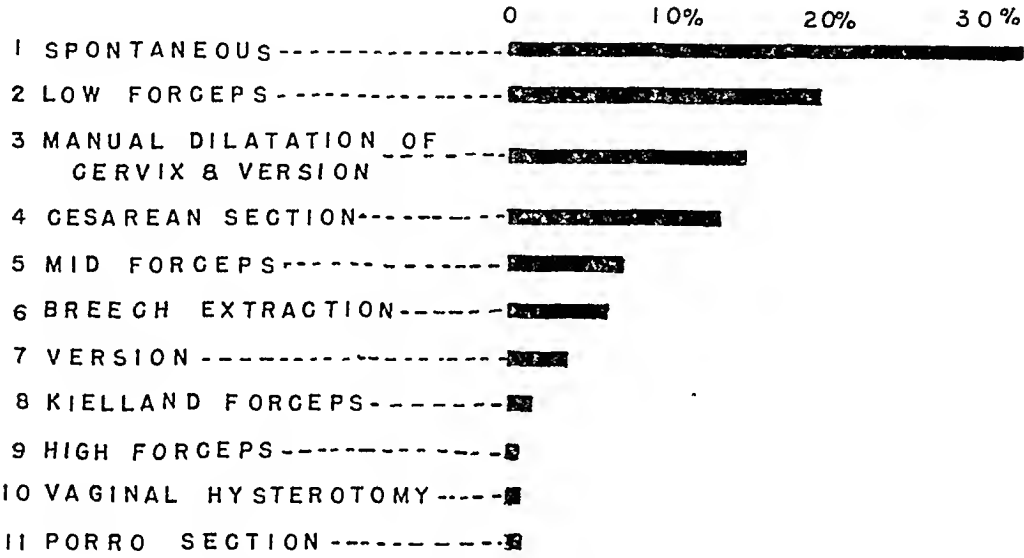


Fig. 4.—Type of delivery; percentage distribution.

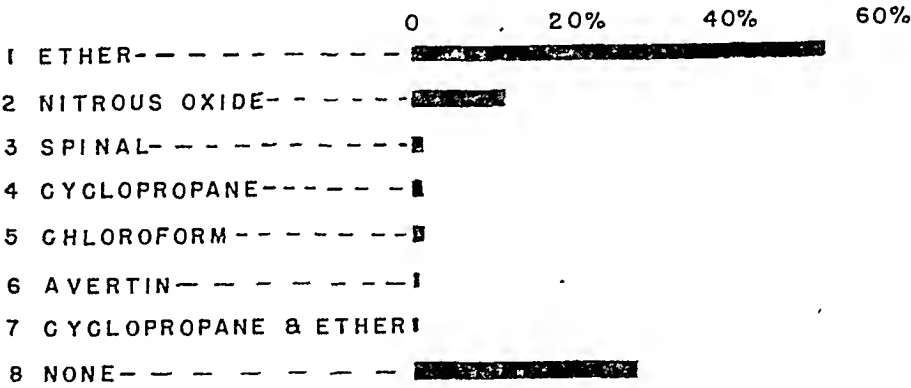


Fig. 5.—Anesthesia; percentage distribution.

Type of Anesthesia

In Fig. 5 we show the percentage distribution of the various anesthetic agents used in the 168 cases. It is interesting to note that 29 per cent of the patients had no anesthesia and as previously pointed out 33 per cent delivered spontaneously. This is scant difference. Therefore from our figures, one could state that a patient delivering spontaneously without anesthesia is just as liable to hemorrhage as the patient with an operative delivery and general anesthesia. Unfortunately, we have no data on regional anesthesia, there being only two cases where spinal was used. The fact that local, caudal, and essentially spinal

used in 12 per cent. In 61½ per cent of the cases the attending physician could not explain to the Committee's satisfaction why the patient had vaginal packing only.

Hystereetomy was used in 6 per cent of the cases. In general, this group received energetic, organized, and recognized therapy. They were patients getting blood, adequately packed, bleeding through their packs and shock deepening. It would appear that the operation increased shock and hastened the fatal outcome, probably because the amount of blood given was insufficient.

### Clinical Picture

The average time between delivery and death from postpartum hemorrhage was five and one-half hours. There was usually ample time for adequate treatment. All too often continuous "seepage" or "oozing" of blood from the introitus went unnoticed by attendants, the proper diagnosis only being made when the patient slipped into shock.

### Discussion

*Prophylaxis.*—Study of these 168 case reports of postpartum hemorrhage reveals many factors overlooked and too often gross carelessness. One of the glaring omissions was good prenatal care. We think of ourselves as administering the prenatal period with utmost care in Philadelphia. Private doctor and free clinic alike saw the patients a regulation number of times and classified their care as adequate. How much time was spent in diet instruction as a means of physically conditioning the patient for her ultimate labor? There was ample opportunity with these patients since 96 per cent had supposedly adequate prenatal care. A few case reports mentioned the general physical condition of the patient as "poor," yet neglected to say in what manner it was poor.

In the prevention of many obstetric—not to mention fetal—complications, the best possible nutritional state is essential. Evidence of appreciation of this factor is lacking in this series.

An integral part of nutrition is the blood picture. Most of the charts carried no notation as to the blood count during the prenatal period. In other instances where a blood count was done, and medication for anemia prescribed, no follow-up studies were done. The patient entered labor without the physician having any idea what the hemoglobin and red blood cell count were. We have seen all of the well-known preparations for combating the anemia of pregnancy fail utterly in correcting this condition. In such instances, there is only one way to prepare such a patient for labor, and that is transfusions in the last four weeks of gestation.

This entire series is impressive from the standpoint of almost total disregard for the necessity of combating anemia in pregnancy as an aid to the treatment of a possible postpartum hemorrhage.

A third factor in the prophylaxis of hemorrhage is routine typing of all prenatal patients. A card is given to all patients during their routine visits, as shown. It is standard procedure to take Wassermanns on all prenatal patients, and it rapidly is becoming routine to do an Rh determination. It is a negligible expense to have the blood typed at the same time. Thus the patient brings the card from the clinic or private doctor with her to hospital admissions when she enters in labor. The saving of time in calling for donors or on the ever ready "blood bank" in an emergency is evident.

Prophylaxis against hemorrhage is carried further in labor. Our Committee records are incomplete on sedation used or its judicious application. There was even less evidence of measures employed to combat fatigue and ex-

## Etiology of Postpartum Hemorrhage

In Table II we have listed the apparent causes of fatal hemorrhage. Seventy-two per cent of the cases fell into the atonic uterus group. Why the uterus was atonic could not be determined, except in those patients having placenta previa, an abruption, twins, or hydramnios.

There were 11 cases of inversion of the uterus. The inversion was usually complete, although there were two partial inversions diagnosed at autopsy. None of these had the uterus replaced. One institution leads the others in this complication.

Overdistention of the uterus from either multiple pregnancies or hydramnios is generally conceded to be a very important cause of postpartum hemorrhage. This was not borne out in our study. Possibly the expectation of hemorrhage in such cases led to careful planning and complete treatment, with a lowered resultant death rate in these patients. Data on that score is not available, however.

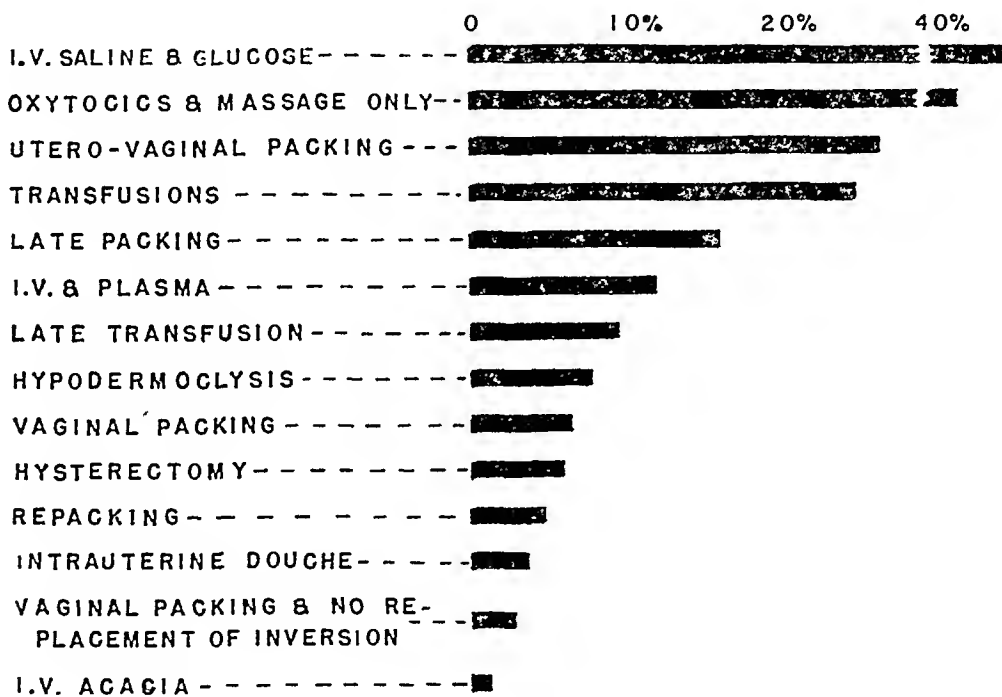


Fig. 7.—Treatment; percentage distribution.

## Treatment

Fig. 7 lists the active treatment given these fatal cases. It is worth while to consider the therapeutic measures employed in detail, remembering that many patients received several of the listed instruments.

Forty-one and one-half per cent of the patients were allowed to bleed to death with nothing more than uterine massage and oxytocics being used. Forty-four and one-half per cent received intravenous fluids, while 25 per cent received blood transfusions. Essentially the same patients received blood as were packed in the orthodox fashion.

Late packing when the patient was practically moribund was used in 16 per cent, while by the same criteria late transfusions found employment in 9½ per cent. It might be interjected here that only two patients were given more than 500 c.c. of blood before death. Plasma, although a partial substitute for whole blood, certainly seems indicated until blood is available; yet it was only

Montgomery advocates a technique that we have followed for some time and have found to be a most reliable method of forestalling postpartum hemorrhage in previa cases. The vagina is packed tightly at the time the patient is examined prior to section; at cesarean section the uterus is tightly packed. Thus the lower segment is held securely between two packs. With adequate amounts of blood the Montgomery method has given the best results we have yet seen. The Committee has not had a mortality report where this method was used. The deaths from abruptio placenta as those from placenta previa were negligible when the patient had been packed and received adequate blood.

Treatment in the majority of cases was far from ideal. First, there was the failure to utilize oxygen. Second, uterovaginal packing was used in only 26½ per cent of cases. Third, transfusions were given to only 25 per cent of the patients at a time when it could help. The amounts of blood used were inadequate, since the average was only 500 c.c. The Committee feels that these measures more than anything else are important in combating hemorrhage. It is understood that oxytocics, Trendelenburg position, stimulation, etc., are in order, but cannot compare with the three major forms of treatment.

Transfusions of whole blood are essential to the saving of life. We have seen the failure of small amounts as employed in this series, and, for the most part, they constituted token resistance only to the threat of death. It must be remembered that blood must be replaced in amounts lost. We have seen cases where as much as 3,000 c.c. were required before a patient could maintain her pulse and blood pressure without continuous oxygen, and at that time be considered out of danger from further hemorrhage.

### Conclusions

Postpartum hemorrhage death was caused by several factors in most cases. They may be summarized as:

1. Carelessness.
2. Inadequate prenatal care.
3. Inadequate care during labor or operation.
4. Ill-advised operations and meddling obstetries.
5. Poor choice and use of anesthesia.
6. Poor management of the third stage of labor.
7. Failure to recognize hemorrhage in time.
8. Insufficient use of oxygen, packing, and whole blood to combat hemorrhage.

We are indebted to Dr. J. Marsh Alesbury for permission to use the committee records, to Miss Dorothy Malhiel for supplying the vital statistics of Philadelphia, and E. E. Schwartz, Children's Bureau, for supplying the National figures.

GERMANTOWN PROFESSIONAL BUILDING

GREENE AND COULTER STREETS

### Discussion

DR. G. D. ROYSTON, St. Louis, Mo.—I am surprised that so few of Dr. Beecham's cases were attributed to the anesthesia given.

My remarks will be directed to those cases of postpartum bleeding that predispose to complications following delivery. It is in this particular group that I feel inhalation narcosis is the most common cause. Among more than 35,000 deliveries on our obstetric service at the Washington University School, the great majority of them purely normal cases, chloroform was administered for the immediate delivery and repair. Naturally, it is not used in toxemic, dehydrated, or other abnormal conditions.

DEPARTMENT OF  
Obstetrics and Gynecology  
Temple University Hospital

Name \_\_\_\_\_

Date \_\_\_\_\_

Blood type \_\_\_\_\_

Rh factor \_\_\_\_\_

Important: Keep this card in your purse. In a present or future pregnancy, or in the case of receiving a transfusion, its information is important.

haustion. From the Committee findings it is safe to assume that little attention was directed at these important factors.

In our search for factors contributing toward postpartum hemorrhage let us next consider anesthesia. It is generally conceded that deep inhalation anesthesia relaxes the uterus, yet I am sure all cases were not carried into a deep plane. It must be remembered that 49 patients delivered without anesthesia. Lacking more complete figures on regional anesthesia one cannot draw a conclusion. Individual case analysis, however, usually demonstrates that there were many errors in any given case with anesthesia adding to the grand total of mismanagement.

Management of the third stage of labor has been the subject of many noteworthy papers. Its importance in general prophylaxis against hemorrhage is well known. We cannot go into all the different techniques advocated by many careful observers for the management of the third stage. Here are some of the obvious errors picked up by the Committee's work:

1. The patients would deliver and the attendant would leave the third stage to some intern or nurse, inexperienced in the signs and symptoms of hemorrhage.
2. Inhalation anesthesia was continued, uninterrupted, through the third stage, although the patient was bleeding excessively.
3. Constant palpation of the uterus or holding of the fundus was not practiced in many instances.
4. In 12 cases the placenta was allowed to remain in the uterus while the patient bled to death, and nothing more than suprafundal pressure was used.
5. In 11 cases inversion of the uterus with no replacement or adequate fortifying treatment occurred.
6. Immediately after delivery of the placenta, the minimum one-hour period of close observation in the delivery room was not carried out.
7. Many patients bleeding abnormally after the placenta was delivered did not receive immediate packing and further measures of control. They were treated energetically only when shock was imminent.

In discussing the etiology of any of these fatal cases of postpartum bleeding, it would seem presumptuous to ascribe a single cause of hemorrhage. There were 75 instances of bleeding from an atonic uterus. What made the uterus atonic would in most cases add up to multiple factors ranging from inadequate prenatal care to choice of anesthetic. The atonic uteri encountered in placenta previa are to be expected from the flaccid lower segment. Once the correct diagnosis was made in placenta previa cases the physician usually forgot that he was dealing with an area in the uterus that is well known for its lack of contractile power. Such being the usual behavior of the lower segment, it would seem expedient to pack all cases, whether they are delivered vaginally or by cesarean section.

We have found nothing in patients who were packed to support the claim that packing increases the incidence of puerperal sepsis. It is surprising to note that many students are taught that packing leads to sepsis. These same students as encountered in National Board Examinations will try to stop hemorrhage by the formidable procedure of putting clamps on the uterine arteries through the lateral vaginal fornices.

Dr. Montgomery has made two important contributions to the prophylaxis of hemorrhage, i.e., the two packs for placenta previa and the "blood type card."

There is another point in prophylaxis that has not been mentioned, i.e., the routine use of whole blood during cesarean section. It is a rule in our hospital along with many others that a patient must have intravenous fluids running, and blood in the operating room before the section is started. This precludes the sudden shock and collapsed veins one occasionally sees in cesarean sections. This has been a most valuable prophylactic step.



All inhalation narcoses and many local means for analgesia require expert administration for satisfactory results. The fear instilled and the lack of training in the proper administration of chloroform are to be deplored.

Most anesthetists, whether physicians or from a school of anesthesia, know little or nothing of its use in obstetrics. Two or three cubic centimeters dropped slowly on the open mask should suffice for the average delivery and repair. Among 4,000 consecutive deliveries under ether, carefully studied and analyzed, 16.6 per cent of the infants were more or less apneic at birth. Where ether is given for delivery, either the patient failed to get satisfactory analgesia, or she was given too much ether and lost too much blood. Among all the anesthetic or analgesic agents employed, ether administration was followed by the highest incidence of postpartum bleeding, if analgesia was attained.

DR. ROLAND S. CRON, Milwaukee, Wis.—I wish to mention an additional possible cause of late postpartum hemorrhage. In the past, large doses of stilbestrol have been administered to relieve the engorgement of breasts during the weaning period. We have seen more and more patients experiencing profound and sometimes exsanguinating hemorrhage following the administration of 15 mg. to 20 mg. of the drug on the third to the sixth postpartum day. Bleeding occurred three to four days later. Curettage and packing were necessary to control the hemorrhage. The curettings showed no evidence of retained placental tissue and only degenerated muscle and blood vessels.

We suspect that the stilbestrol may have some effect upon the end arteries and we know that there is a lag of two to three days between the time of administration and the bleedings from the arterioles. Since stilbestrol therapeutics is questionable in its efficacy for the relief of breast engorgement, and since postpartum hemorrhage may be associated with its administration, we suggest the discontinuation of its frequent use during the postpartum period.

DR. FREDERICK H. FALLS, Chicago, Ill.—There is one prophylactic measure that we have developed in Chicago in our clinic which we feel is of some value. We supply our patients with a tag, similar to the dog tag used in the army, stating the Rh factor and also the blood type. The patient wears this until she has been delivered. In case a patient has a bad acute or postpartum hemorrhage and is taken into an institution where her laboratory record is not available, at least her Rh factor and blood grouping are known.

DR. IRVING W. POTTER, Buffalo, N. Y.—I would like to talk particularly about our own management of these cases. We pay particular attention to the anesthetic, and for years we have dwelt persistently on the use of chloroform. Now it is an unfortunate matter when you consider that the young man who gives the anesthetic in the average hospital has probably never had a bottle of chloroform in his hands. Just as Dr. Royston has told you, they are afraid of it; and I am very sorry to feel as I do toward the teachers of anesthesia, that they are neglecting to teach these individuals the intelligent use of chloroform. It has been my experience that if you want to get a good chloroform anesthetic, you have to get the older man.

There are other things to be considered, and one is the management of the third stage of labor. It is surprising to watch men finish up the third stage. If you wait, the placenta will slide out of the vaginal canal with very little bleeding.

DR. BEECHAM (Closing).—There has been much discussion concerning anesthesia. I must admit a deep prejudice against general anesthesia in obstetrics and gynecology. A review of the 168 records failed in the main to establish general anesthesia as the single etiologic factor in postpartum hemorrhage where it was employed. Rather, multiple factors along with poor choice and administration of a general anesthetic seemed to be the causative agents.

Dr. Royston emphasized rapid packing of a bleeding uterus. We are certainly in accord with this procedure. Packing is best employed when the bleeding has been present several minutes with no sign of decreasing, and before there is an alteration in pulse rate.

diet based on that number of calories (usually from 1,300 to 1,500 calories), and is asked to eat everything served her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. After five to six days the caloric content of the diet is increased by another 300 calories. For a few days discomfort after eating may again appear. This procedure is repeated until the caloric intake is between 3,400 and 3,600 calories.

The behavior of the basal rate of metabolism usually is typical when these patients respond to the above regime. Many of them have rates well below -20 per cent, some as low as -35 per cent. Coincident with the gain in weight the rate of metabolism will return to normal without the administration of thyroid extract. Indeed, this medication is poorly tolerated and actually may impede recovery of these patients.

It must be kept in mind that most of these young women suffering from anorexia nervosa previously had been healthy and had experienced normal menstruation. Evidence of malfunction did not appear until the glands of internal secretion concerned with menstruation were deprived of a normal internal environment. Until there is return to a normal nutritional state, and thus a normal environment, we may not rightly expect functional activity of these glands. When such a state has been reached and menstruation has not recurred, we may then commence hormonal or other therapy aimed to further stimulate function. The cyclic administration of estrogens may, however, be commenced as soon as feasible in an attempt to shorten the period of uterine atrophy usually seen in these patients.

### Cyclic Therapy With Estrogens

Where there has been considerable reduction in the size of the uterus, and particularly when microscopic examination of the endometrium reveals atrophy, it is advisable to commence the cyclic administration of estrogens, either for two or for three weeks in four. This can be accomplished with various preparations. One of the simplest methods is to use diethylstilbestrol to the daily limit of tolerance. Other preparations for oral and parenteral administration, of course, can be used. This form of treatment serves at least three purposes. First, it primes the uterus and endometrium and tends to prevent further atrophy. Second, stimulation of the pituitary body may be encouraged by simulation of the cyclic rise and fall of bodily estrogens that occur under normal conditions. A more complete imitation of this may be achieved by combining estrogens and progesterone in the therapeutic program. Third, if adequate amounts of these substances are used, and the uterus and endometrium make no response, we may assume that the Müllerian duct is naturally unresponsive and therefore may be a contributing factor to the amenorrhea.

The presence of estrogens is responsible for the distinguishing characteristics of women, and for the integrity of the physiology of the menstrual and reproductive cycle. Therefore, it seems desirable to attempt to restore levels in the body to within normal limits as soon as possible.

## THE TREATMENT OF AMENORRHEA IN YOUNG WOMEN\*

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THE conditions associated with the occurrence of amenorrhea lasting from one to five years in 94 women between the ages of 19 and 25 years were discussed in a previous paper. These conditions were tumors in seven cases, anorexia nervosa in 15, failure of the pituitary body in 36, failure of the ovary in 17, and primary amenorrhea in nineteen. The seven patients in whom tumors were found are excluded from consideration in this paper, leaving 87 patients whose treatment is to be discussed herein. The importance of the history, physical examination, and various laboratory tests was emphasized in determining the reason for the amenorrhea and classifying the deficiency. This seems of great importance. One is often asked for advice in the treatment of a patient who has amenorrhea. I doubt that one may safely generalize without knowing as much as possible about the given patient, and then treatment becomes individualized for that patient. For example, treatment with roentgen rays to the pituitary body or with extrinsic gonadotropins for a woman who has excess amounts of prolactin in the urine, or who clinically presents the picture of menopause praecox, is not rational.

The procedures to be mentioned herein represent those employed in the treatment of the aforementioned group of 87 young women.

### Nutrition

Nutrition assumes great importance in all bodily functions of the young person. One frequently finds some disturbance of the function of menstruation in women who are considerably under- or overweight. The extreme example of variation in weight associated with menstrual disturbances is seen in the patient suffering from functional anorexia or anorexia nervosa. These patients should serve to emphasize the basic necessity of a balanced ration rich in proteins and vitamins. The tissues concerned with the menstrual function in the young seem particularly sensitive to deprivation of these elements. When the patient is markedly underweight or anorexia nervosa exists, it must be remembered that a daily caloric intake well above the daily caloric requirement for that particular patient must often be maintained for several months before the patient regains her normal weight. Young women suffering from anorexia nervosa have so restricted the quantity and quality of their intake of food that the patient and her gastrointestinal tract must be re-educated. Our procedure for the treatment of this condition has been outlined by Berkman<sup>1</sup> as follows:

An estimate of the patient's previous daily caloric intake is made. To this amount is added 300 calories. The patient is served a high-protein, high-vitamin

\*Read before the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

investigations of Drips<sup>2</sup> and Ford eighteen years ago. We have found that these treatments often would re-establish the menses, but the effect frequently wore off in a few months and needed to be repeated. It is also apparent that better results are obtained when amenorrhea of more than a year's duration is due primarily to pituitary rather than to ovarian failure. Dr. Drips, for example, has among her records those of twelve young women\* whose amenorrhea of one year's to ten years' duration was attributed to failure of the pituitary body and who received only roentgen therapy to the pituitary body and ovaries. Seven of these patients experienced menstruation for a year at least, and two for a shorter period, an improvement rate of 75 per cent. Twenty-three young women who had amenorrhea of one year to seven years in duration due to ovarian failure were likewise treated with roentgen rays to the ovaries. Five of them improved for a year at least, and four were benefited for a shorter period, an improvement rate of 39 per cent.

When a lowered rate of metabolism is found in these patients, the rate is purposely elevated before the roentgen treatment, and, when the menses reappear, estrogens are administered cyclically. This combined therapy has been more successful than any single method.

In a group of 55 single women\* of an average age of 22.5 years treated between 1930 and 1940, 21 were still single in 1945, and 14 (66.6 per cent) of the 21 were still having regular menses. Thirty-four had married and 26 (76.4 per cent) of these 34 reported their periods were still normal in 1945. These 34 women had already borne 38 normal children and had experienced two misearriages. A few of the women had reverted to their previous status of amenorrhea after parturition.

### Extrinsic Gonadotropins

Extrinsic gonadotropins have been but rarely employed by our group. Only three of the 87 patients concerned herein received them. We have preferred to make every effort to stimulate the patient's own pituitary body. If this can be done, certainly a more effective gonadotropin is produced. No doubt gonadotropic preparations have a place in the treatment of amenorrhea, as evidenced by the reported work of others.

### Results of Treatment

Eighty-seven patients who had experienced amenorrhea for a year or longer were treated by combinations of the methods previously discussed in this paper. The follow-up period for this group of 87 patients has ranged from one year to six years, with an average of two years and three months.

Seventeen of the 87 patients experienced amenorrhea because of failure of the ovary to function; in 10 (58.8 per cent) of these 17 the menses reappeared after treatment.

Thirty-six of the 87 patients experienced amenorrhea associated with failure of the pituitary body; 26 (72.2 per cent) of the 36 responded to treatment.

\*Not included in the present series of eighty-seven.

### Thyroid Extract

The relationship of thyroxin to the physiology of the genital tract is not definitely known, except that the general efficiency of the body is enhanced when sufficient amounts of this substance are present in the body. Accordingly, the efficacy of thyroid extract in the treatment of amenorrhea in properly selected cases is widely recognized. However, there are certain important considerations that should be discussed.

One should be certain to determine the patient's actual basal level of metabolism before initiating treatment. Often more than one estimation of the rate is necessary. When this has been determined, one has a point from which controlled treatment can be commenced and followed through by repeated estimations during the course of treatment.

As a rule, we prefer to elevate the rate rather abruptly. For example, with a basal metabolic rate of between minus 15 and minus 20 per cent, the patient is given 3 to 4 grains (0.19 to 0.26 Gm.) of desiccated thyroid substance for three days, 2 grains (0.13 Gm.) for three days, and then 1 to 1½ grains (0.06 to 0.1 Gm.) daily. Another basal metabolic rate is taken after the first week of treatment, and another after the second, after which it is usually possible to determine the maintenance dose. Occasionally, a longer period is necessary.

The patient is then instructed to be certain that the same brand of thyroid substance is always used, and is told that estimations of the basal metabolic rate are advisable from time to time for proper control of treatment. If any untoward symptoms seem to occur, the patient is asked to report. It is emphasized to that patient that the daily maintenance dose is to be continued indefinitely. Several months may elapse before the full effect of the readjustment of the basal metabolic rate will be effective.

The normal range of basal metabolic rates is stated to be between +10 and -10 per cent, and if a given patient's rate is within this range, treatment with thyroid extract frequently is not considered to be necessary. Often this is true. However, properly controlled treatment with thyroid extract offers a very effective and safe method of stimulating bodily function. Consequently, even if the basal rate is within the limits of -10 and zero in the presence of amenorrhea, elevation of the rate to +5 per cent may be considered, if it is properly controlled. If symptoms of intolerance occur and persist, the treatment can be stopped. I have seen instances in which elevation of a rate from -15 to -5 per cent was ineffective, but in which satisfactory results occurred where the rate was elevated further to +5 per cent.

In the presence of a lowered rate of metabolism or one that has been inadequately elevated, other forms of substitutional or stimulating therapy frequently are ineffective. Accordingly, we usually postpone other forms of treatment until the basal metabolic rate has been stabilized within normal limits. Frequently, when this occurs, no other treatment is necessary.

### Roentgen Therapy

Low dosage roentgen-ray irradiation to the pituitary body or ovaries, or to both, has been employed safely and effectively at the Mayo Clinic since the

Though most of us have been reluctant to use irradiation, our experience at Indiana has, like Dr. Randall's, been encouraging. Dr. J. A. Campbell, our radiologist, has treated 24 cases of amenorrhea and sterility. All had had endocrine therapy and had not responded. These were given low dosage irradiation to the pituitary and ovaries. Normal menstruation followed in 17 cases. Three of these have delivered normal babies and a fourth is now pregnant. Treatment failed in 7 cases.

It is significant, I think, that the highest percentage of successes in Dr. Randall's cases were in those of pituitary failure, particularly as extrinsic gonadotropins were rarely used.

Finally, from the standpoint of the practical clinician, Dr. Randall has given us light and encouragement instead of the fog and contradiction often present in endocrinologic manuscripts. While the present-day treatment of amenorrhea is far from satisfactory, we need not be too pessimistic in undertaking it.

DR. WILLIAM R. BARNEY, Cleveland, Ohio.—I would like to ask about pregnancy following this treatment in Dr. Randall's cases?

DR. RANDALL, Rochester, Minn. (Closing).—In reply to Dr. Barney's question in regard to pregnancy following the treatment of amenorrhea, may I point out that the patients here discussed are all young, and very few of them are married. Consequently, the number of patients in whom pregnancy was a possibility is too small to warrant any conclusions.

Fifteen of the 87 patients experienced amenorrhea in association with anorexia nervosa; eight (53.3 per cent) of the 15 responded to treatment.

Nineteen of the 87 patients had primary amenorrhea; three of the 19 (one aged 19, one aged 21, and one aged 23 years) began to have menses after treatment.

One should not accept these figures too literally. In another group of 87 patients better or poorer results might be obtained. One must apply himself to evaluation of the status and treatment of the individual patient.

### Conclusions

We will agree that in these young women with established amenorrhea, every reasonable effort should be made to salvage the menstrual and reproductive functions. This salvage will never occur in 100 per cent of these cases of amenorrhea of long standing. Consequently, if an intensive trial of treatment is not successful, it may well be stopped. If the patient's own glandular functions will not carry on after therapy has been thus halted, little will be gained by further treatment.

It is well known that in general the shorter the duration of the amenorrhea, the better will be the response of the patient to treatment. The condition of those patients who present amenorrhea of less than a year's duration, therefore, offers a better prognosis as a rule than that of the group reported herein.

The aim of the plan of treatment outlined in this paper is, first, to secure an environment or general bodily condition in which the nonfunctioning or poorly functioning glandular tissues will have the best chance for function. Second, when this has been secured, effort is made to stimulate function and to maintain it.

### References

1. Berkman, J. M.: *Ann. Int. Med.* 22: 679, 1945.
2. Drips, Della G.: Personal communication to the author.

### Discussion

DR. GERALD W. GUSTAFSON, Indianapolis, Ind.—Individualization of the patient with correction of dietary deficiencies, general ill health, and anemias before institution of endocrine therapy seems rational. The recognition and correction of hypometabolism, hypo- and hyperthyroid states before other endocrine therapy is begun also seem advisable. When indicated, thyroid gives more brilliant results than any other endocrine substance, and often is sufficient therapy.

If the general health and metabolism of the individual are normal, it is then ideal to attempt to catalogue the patient as to whether there is ovarian or pituitary failure or a possible adrenogenital syndrome.

In cases of ovarian failure with atrophic endometrium, reduction in size of the uterus and with high urine gonadotropins, cyclic treatment is warranted. Recognizing that estrogens are merely substitutional, they are, as Dr. Randall has stated, necessary to prime the endometrium. It is probably ideal to follow with progesterone and Zondek, Rakoff, and others have reported encouraging results with large doses of progesterone. When the latter is given in large amounts, such as 20 mg. daily for three days, estrogens can be given for a shorter time with less tendency to inhibit the anterior pituitary. Rakoff recently reports improvement in the hormonal pattern, even in cases of gonadotrophic deficiency.

tingencies it could reasonably be assumed that the agglutinin might fall in titer, or even disappear temporarily. Facts support these arguments.

There are so many variants involved that only in a comparatively few cases does the true mechanism reveal itself. These variants, if not envisaged, may mislead one in drawing conclusions from statistical data, however extensive the data may be.

From the disease standpoint, we are not dealing basically with agglutinogens and agglutinins, but with toxic substances and antitoxic substances. This concept of fetal toxins and maternal antitoxins furnishes a reasonable explanation of why it is that the group O mother inherits the anti-A and anti-B agglutinins: the group A mother, the anti-B agglutinin; and the group B mother, the anti-A agglutinin.

The antitoxic substance inheritance provides a modicum of protection for the mother, and operates against her interests, spelling her likely doom only in the event of gross transfusion of incompatible blood, a contingency that was not envisaged by nature.

If this be true, the question as to why the human possesses hereditary antitoxins against some substances and not against others would seem to be reasonably answered conjecturally by an ontogenic approach. At least the A and B substances, against which antitoxins are inheritable, can be demonstrated, according to Kemp, about the thirty-seventh day of gestation, and yet, the fetus' own complement of antitoxins does not appear until around the two hundred and eightieth day. It may be argued with reason, it would seem, that one can infer from this that it takes in the neighborhood of eight times longer for a specific antitoxic substance to become inheritable than for a cell substance to become inheritable. It may be that the substances against which no inherited antitoxins obtain may have entered the species too recently to permit of their specific antitoxins being yet inheritable. This would include the Rh group.

Adequate proof of a toxin-antitoxin relationship between child and mother with the involvement of disease demands that one isolate in the child a substance not possessed by the mother; that one demonstrate that she reacts to this specific substance either by the active production of an identifiable specific antitoxin where no antitoxin previously obtained, or by a functional change in titer of a pre-existing antitoxin; that during this process signs of disease manifest themselves in the mother, signs that follow a characteristic pattern, and that seem to bear a direct functional relationship with the toxin; that the severity of the manifestations of disease vary in inverse proportion to the demonstrated strength of the antitoxin; that after separation of the child, which separation removes the main source of the toxic insult and the antitoxin absorptive power of the child, the rapidity of recession of signs of toxemia tend to vary in direct proportion to the rise of antitoxin strength as occurs in snake venom poisoning, according to the amount and strength of the antitoxin administered; and that the infant may be injured or killed if the antitoxin becomes too strong and attacks the cells of the fetus, whose cells contain the same toxic substance which has demonstrably provoked the antitoxin formation.



## SEROLOGY AND OBSTETRICS\*

R. T. LAVAKE, M.D., MINNEAPOLIS, MINN.

EXPERIENCE acquired in quest of the cause of the toxemias of pregnancy would seem to suggest that we revise our interpretation of the significance of agglutinogens and isoagglutinins in the blood setups.

Due to the tremendous importance of blood transfusion as a therapeutic agent, attention has been focussed upon the agglutinogens and isoagglutinins from the gross transfusion standpoint, and with too little regard for their possible association with disease manifestations, which latter would seem to be due to nature's method of breeding cell substances in or out of the human species, in the inscrutable interests of evolution.

It is well understood that the possible death of the recipient of incompatible blood is due to the agglutination of the donor's cells by the action of the agglutinins of the blood of the recipient. It is not generally sensed that such incompatible blood may be actually poisonous to the cells of the recipient, and that, if the obscuring effects of agglutination and hemolysis could be obviated, we would note pathology in the recipient similar, in kind, to that found in the toxemia of pregnancy. This can be glimpsed, occasionally, in cases of delayed transfusion deaths, and even in disease manifestations following the intramuscular injection of, here defined, toxic bloods.

In nature, the nearest approach to transfusion occurs at times and in infinitesimal quantities between fetus and mother, and it seems evident that the blood setups are the evolutionary results of this contingency and possible filtration of antigens. The result presented would seem to point to the validity of the argument that the inherited agglutinins represent inherited antitoxic substances which constitute a modicum of protection for the female, who may, under the bisexual mechanism of propagation and under the laws of heredity, bear a fetus containing blood substances ancestrally and presently toxic to the type of cells that she possesses. These agglutinins are, as in bacteriology, merely one of the functional arms of antitoxic substances, the other arms being the lytic and opsonic. When you titer an isoagglutinin, you are titering the strength of the antitoxic substance from which it stems, and, as will be suggestively demonstrated later, if the antitoxic substance involved is not of sufficient strength to protect the mother, and if her cells are vigorous, they will secrete more of the same antitoxic substance, and the titer of the isoagglutinin may rise. The statement may rise, is used advisedly, and should be emphasized, because the true strength of the antitoxin may be masked by the antitoxin absorptive power of the fetal cells and antigens in solution; and again it can reasonably be assumed that it would not rise if the maternal cells were deficient in reactive vigor, or were overwhelmed. Under a combination of such con-

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

where it did not exist could not be duplicated. In fact, there did not appear to be a significant increase of toxemia in those bearing incompatible children when compared with the cases of toxemia in which the children were compatible. From this data it seemed that upon the basis of incompatibility alone the hypothesis was untenable.

Because of this evidence, a maternal intradermal skin test was devised, designed to give evidence, by prediction, that a toxin came from the fetus and that the mother was immunized to this specific toxin. Though the results of this test converged in evidence of the high degree of probability of the hypothesis, the test in no way identified the nature of the suspected toxin, and the test could be made only after the birth of the child.

Then came the discovery of the Rh factor by Landsteiner and Wiener, the disclosure, by Wiener and Peters, of the danger of isoimmunization by this factor in transfusion, and the work of Levine, Katzin and Burnham, showing the relationship of this factor to erythroblastosis fetalis, abortions, stillbirths, and macerated fetuses. This work seemed to complete the whole circle of the classical and largely accepted toxin-antitoxin mechanism, enunciated by Ehrlich. In these cases of clinical erythroblastosis the correlation of an accompanying toxemia is about 30 per cent, which is significant, as it is far above the average incidence of toxemia in general from whatever cause. This would seem to logically mark the Rh substance as a toxin when it can gain access to a host not possessing a similar substance by heredity. Furthermore, since antibody studies have been made on suspicion of the possibility of beginning isoimmunization, several of these cases have shown beginning isoimmunization not severe enough to give evidence of fetal injury at birth, and yet some of these mothers have shown clinical evidence of toxemia. Again, from the third case exhibited below, it would seem likely that in the cases of erythroblastosis not showing toxic symptoms in the mother, the antitoxin is so strong that it protects the mother while injuring the child. Philosophically, from what is known about snake venom and bacterial toxemias, it would seem hardly credible that any substance toxic enough to provoke the formation of an antitoxin that could injure or kill the fetus could so function without at any time producing some clinical manifestations of disease in the mother, unless she were thoroughly protected by the antitoxin. Possibly some almost subclinical manifestations are being overlooked.

It soon became evident that the A and B substances could bring about the same train of phenomena when the Rh status of fetus and mother were similar, thus placing these substances under the definitions of toxins. This became increasingly evident when the agglutinin titers were followed both before and after the separation of the fetus.

It seems now that when one can prove from the blood status of husband and wife that the child may inherit one or more of the three substances, A, B, Rh, of a type not possessed by the mother, that woman should be watched with especial care. Even though both mother and child are protected by various proved safeguards, at times, mother, child, or both, may be injured or killed in the toxin-antitoxin battle.

The last demand has been adequately satisfied according to this viewpoint by the work of Levine, Katzin, and Burnham, Javert, and many others. As an aside, it may be interesting to know that, pursuing this line of thought, it was argued by analogy and prediction that if the mother's antitoxin could injure or kill her child, one should be able to kill a rattlesnake by the injection of the antitoxin specific to its toxin. Not being able to obtain any information on the subject, this was tried with the aid of Dr. W. J. Breckenridge, director of the Museum of Natural History of the University of Minnesota. After first testing a rattlesnake for serum reaction, a dose of anti-toxin was injected which was deemed adequate to protect a human from the bite of a moderate-sized rattlesnake. In fifteen minutes, every muscle of the snake became convulsed, the snake assumed a cartwheel attitude, snapping convulsively at its vibrating rattles, and, after intervals of apparent recovery, died in eighteen hours.

The cells of the vital organs showed pathology. There was a functional relationship between the size of the snake used, the size of the dose of antitoxin, and the severity of gross reaction and microscopic destruction. This work is being conducted to determine whether, after prolonged administration of sublethal doses of antitoxin, basic lesions would obtain as may obtain in an erythroblastotic child that is ostensibly cured by blood transfusion. It has become a grave question with many whether one is justified in subjecting a mother to whatever danger resides in a cesarean section, to obtain a child that has only a slight chance of life, and, if it is saved, may be cruelly handicapped by basic lesions.

When this serologic exploration was begun in 1919, the findings soon seemed so adverse that it was discontinued. When, in 1923, McQuarrie published his article in corroboration of the theory that incompatibility of blood might be the cause of pregnancy toxemia, his arresting findings were considered due to the element of chance sampling. At that time, of course, the A and B agglutinogens and the anti-A and anti-B agglutinins, considered merely as characteristics but involved in blood incompatibility, were alone envisaged. Under the same conditions, a resumption of investigation showed that for every woman who developed toxemia while bearing an incompatible child, a like case would be found showing no sign of toxemia. It seemed that one need not waste time multiplying these findings by any large figure to come to a conclusion that incompatibility was not likely the cause of toxemia. However, as variants were disclosed, such as: whether the mother, child, or both were or were not secretors; the question of placental integrity; and especially the possibility of viewing agglutinogens as structural parts of basic toxic substances, and agglutinins as one arm of inherited antitoxic substances, the findings took on a different significance and former arguments derived therefrom became fallacies of neglected aspect. If such natural protections could be reasonably assumed, it then would seem highly significant that in 50 per cent of mothers bearing incompatible fetuses, toxemia would be manifest. The most damning evidence against the probability of incompatibility as a factor in the causation of toxemia was afforded by the cases in which no incompatibility could be demonstrated. McQuarrie's findings that toxemia was  $16\frac{1}{2}$  times more frequent where incompatibility existed than

Here a reasonable interpretation would seem to be that the antepartum antitoxin strength was kept low by fetal antibody absorption. The latter, in conjunction with marked placental infarction at the front line of the toxin antitoxin battle, likely killed the fetus. As soon as the mother's antitoxin was given a chance to accumulate, her toxic manifestations melted away rapidly. The same course and pattern evokes when one gives rattlesnake antivenom in rattlesnake poisoning.

CASE 3.—A multigravida who gave a history of two previous erythroblastotic disasters. Her anti-A agglutinin titer rose to around  $\frac{1}{8},000$ . No signs of toxemia were obtained, or at least they were not noted. At the age of estimated viability of the fetus, the mother was delivered by cesarean section of an erythroblastotic child, whose immediate life was saved and whose manifest severe lesions disappeared under multiple transfusions. Five days after delivery the maternal anti-A agglutinin titer shot up to  $\frac{1}{8},000,000$  plus. She made an uneventful recovery.

Here we seem to have an example of an antitoxin level that apparently protected the mother but was held deceptively low by the antitoxin absorptive power of the fetus. After separation of the fetus, the true strength of the antitoxin formative power of the maternal cells made itself manifest both by the lesions in the child and by the tremendous increase in the antitoxin titer in the mother.

### Conclusions

In closing, may it be said that the routine knowledge of the A, B, and Rh status of husband and wife has been found to be of more frequent use and of as great value as the routine knowledge of the Wassermann status. As both may be obtained with one drawing of blood, nothing is added to the inconvenience of wife or husband. It gives one a reasoned feeling of security, or at least of preparedness in facing the problems that may ensue. It permits the more accurate segregation of cases that bear special watching. It permits one to be more sure of the matings that will not likely result in toxemia of pregnancy, premature separation of the normally implanted placenta, or fetal injury, death, and abortion due to a toxin-antitoxin mechanism. It permits the building up of available sources of Rh-negative blood of every group to which one may turn in case of need in the interests of mother or child.

Far from engendering unnecessary anxiety, experience proves that the procedure is very reassuring to all concerned. It is amazing how widespread has been the dread aroused in men and women alike, by the articles in the public press and magazines concerning the Rh factor. Men and women alike express relief that their genetic status is being kept in mind, and cooperate enthusiastically in having the tests made. Whatever the findings, one is enabled to quiet inordinate fears and make the patients realize the extreme infrequency of the dire results that they envisage. Where, before, they often resented the implications of the Wassermann, and, now and then the husbands succeeded in avoiding the test, all welcome the genetic test, and as all the tests may be made from one drawing of blood, the Wassermann test need not be mentioned.

### Discussion

DR. J. P. PRATT, Detroit, Mich.—Nearly 50 years ago Zweifel designated eclampsia as "the disease of theories." Presentation of a new theory today indicates that we are

Irregular cross-matching reactions, as well as hiatuses in the fetal toxin evidence of pregnancy toxemia, would indicate that all implicated blood substances have not been found. However, these hiatuses now seem so relatively less frequent that they speak less against a fetal toxin hypothesis and more for either an intensive search for yet unknown blood substances, or for their differential value in diagnosis. Some of these hiatuses may represent true cardiovascular-renal causation, due to vital organ deficiency, either the result of heredity or previous diseases, among which a previous pregnancy toxemia must be included.

Our current accepted forms of pregnancy oversight and treatment have empirically satisfied the therapeutic demands of such a toxin-antitoxin setup: supportive, eliminative, and protective treatment, and separation of the fetus before serious damage has been sustained by mother or infant.

The validity of the main argument is not of mere academic interest. Its main importance lies in the direction that it gives to the possible development of specific antitoxic sera for ready use, in the interests of the mother, either after the intrapartum death of the child or after delivery of a live child, especially in postpartum eclampsia. This direction is being pursued.

Three examples have been chosen for your criticism of the arguments involved. They have been chosen because, no matter what variants are involved, the mechanism seems to stand out clearly. Between the three, all the demands of proof first cited are fulfilled. The mothers were in group O, the husbands in group A, the children in group A, and mothers, husbands, and children were Rh positive. The common denominators, it was felt, permitted a more accurate comparison and interpretation:

### Case Reports

CASE 1.—A primigravida. With the accession of manifestations of toxemia, her anti-A agglutinin titer had risen to around  $\frac{1}{1,000}$ . Her anti-B titer did not rise. It was clinically a low grade toxemia, but required hospitalization around the thirty-fourth week because of a brisk hemorrhage with pain. The condition was checked by pelvic examination and soft tissue roentgenograms, and diagnosed as a minor premature separation, which was later corroborated upon the birth of the child. The bleeding and pain quickly ceased and, with slightly increasing manifestations of toxemia, she delivered normally at term a clinically and serologically normal group A child. Five days post partum, the mother's anti-A agglutinin titer rose to around  $\frac{1}{2,000}$ , and she made a slow recovery.

Here would seem to be an example of a group O mother reacting to an A toxin by the formation of additional antitoxin. Her inherited complement of antitoxin was not sufficient to protect her fully from manifestations of toxemia, nor was it ever strong enough to demonstrably injure the child. The minor increase in the strength of the antitoxin after the birth of the child with its antigen insulting and antitoxin absorptive powers, allowed of only a slow recovery from the manifestations of toxemia.

CASE 2.—A primigravida developed a toxemia accompanied by an anti-A agglutinin titer around  $\frac{1}{1,000}$ . This titer did not increase with increasing manifestations of toxemia. About the twenty-eighth week, the child died in utero, and was delivered. Five days post partum, the mother's anti-A agglutinin titer rose to  $\frac{1}{100,000}$ , with a rapid disappearance of toxic manifestations.

toxic amines may be formed from their respective amino acids in the degenerated chorionic epithelium.) It is well known that there is no longer any place for Welch's "Dietum" in the postmortem finding of eclampsia. These findings are identical with death from toxins and poisons. It is easy to say eclampsia is a disease of theories. Why not check and recheck the things which are known?

DR. LAVAKE (Closing).—Dr. Johnson has answered Dr. Pratt's question regarding hydatidiform mole and pregnancy toxemia.

Dr. Pratt asks how one can associate an agglutinin with a toxin. The realization of such an association has been just as difficult for me to reach as it is difficult for you, because we have all been raised on the same traditional ideas and canons of serology as they pertain to blood groups and blood transfusion. Here, their original brilliance remains undiminished. But they were formulated to meet the demands for a logical explanation for the phenomena resulting from the gross mixture of bloods, a purely artificial procedure.

Though Hopkins, in 1910, and Ottenberg and Kaliski, in 1913, showed that incompatible blood was not only agglutinated by the blood of the recipient, but was hemolyzed, and the red cells devoured by the leucocytes of the recipient, we have always felt called upon to attribute the phenomena not to an antitoxin, as in bacteriology, but to some special properties in blood—a different mechanism, as it were. Now, the findings in maternal toxemia and erythroblastosis fetalis suggest clearly that a toxin-antitoxin relationship here exists between fetus and mother, depending upon differences in cell substances. The agglutinogens stem from these cell substances and thus are associated with toxic substances under the conditions that make the substances toxic to other cells.

It has been asked why, if this be true, we see less toxemia now than formerly. Experience would suggest that this is due to more widespread and better prenatal care, the elimination of focal infections, attention to the prevention of general infections, and more early and intensive treatment: but, experience would add that it is significant that some of the worst toxemias obtain in spite of the earliest recognition and the best treatment.

In answer to the query as to how one can associate an isoagglutinin with an antitoxin when the former is rapid in action and the latter shows a delayed action, it may be said that if one follows isoagglutinin titers following a sublethal injection of incompatible blood, it will be found that it takes about twelve days for the specific isoagglutinin titer to reach its height. It follows the pattern of antitoxin rise in bacterial infection. The rise of the agglutinin titer is one of the indices of the rise of antitoxin strength because it is one of the functional arms of the antitoxin.

still groping for facts and that our knowledge regarding toxemia remains immature. Early theories referred to disorders of the nervous system peculiar to pregnancy. Other early theories referred to bacterial invasion. Williams, in 1903, summarized as follows: "The clinical history and anatomic findings afford presumptive evidence that the disease is due to the circulation of some poisonous substance in the blood which gives rise to thrombosis in many of the smaller vessels, with consequent degenerative and necrotic changes in the various organs. But, at the same time, we are absolutely ignorant concerning the nature of the offending substance, and besides, the experimental evidence thus far adduced in favor of such an etiologic factor is not convincing." Since then advances in metabolic and endocrine studies as well as the discovery of blood groups have stimulated many new theories.

A new proposition is welcome inasmuch as no theory yet proposed adequately explains eclampsia. When no experimental data has been presented, perhaps the best way to establish the value of a theory is to ask questions about it. May I ask how the author justifies using agglutinogens and toxins synonymously? By definition: an agglutinin is any substance which, acting as an antigen, stimulates the production of agglutinin, while a toxin is any poisonous substance of microbic, vegetable, or animal origin which does not cause symptoms of poisoning until after a period of incubation and are antigenic. It seems illogical to use these terms interchangeably, implying that red cells and their agglutinogens are actually poisonous. Further, these agglutinogens do not satisfy the definition of a toxin, as a reaction to them is immediate rather than after a period of incubation. The clinical and pathologic manifestations of toxemia and transfusion reactions are not similar.

The higher incidence of eclampsia with hydatidiform mole indicates that the offending object is the chorion but not the fetus. Incompatibility of the elements of the blood is not possible in such cases for there is only one source for all the blood.

If toxemias are due to hereditary incompatibility of blood of mother and fetus, can this change to compatibility during pregnancy? If not, what explains the improvement in toxemias when given proper prenatal care?

One can heartily agree with the advice to study blood grouping of all prenatal cases, including the husband's whenever possible.

DR. HERMAN W. JOHNSON, Houston, Texas.—Dr. LaVake indicates that there might be some connection between the different blood groups, and especially the Rh factor, of fetus and mother, as an etiologic factor in toxemia. It's an interesting speculation, but offhand one regrets to have the present confusion surrounding the toxemias further complicated by the confusion of the Rh factor. The theory of antagonistic blood groups as an etiologic factor was exploded early in this century. If now the Rh factor has to be investigated there would be slight hopes that it would offer any solution. Naturally it would have to depend on the antigen-agglutinin reactions with all its possibilities. If that were the case, it would be logical to expect the pattern of erythroblastosis to be followed, in which event a sensitized mother would suffer a more severe toxemia with succeeding pregnancies which is not the case, as every clinician knows.

Dr. Pratt has just suggested that we do not know much more about the etiology of eclampsia than we did years ago. I know we do but also know that many of us refuse to accept the known facts. It is known that eclampsia occurs only in the human female, who is the only animal which maintains the upright position. Therefore there is some connection between the venous back pressure of the upright position and eclampsia, and especially when this is combined with primigravida, oversize babies, twins, and polyhydramnios. We know that a placenta has to be present in order to have eclampsia. And in postpartum eclampsia there is a symptom continuity of hypertension from shortly after the expulsion of the placenta up to the time of the convulsion. It is quite safe to say that eclamptic toxemia is impossible either in late hydatidiform mole or in late pregnancy without marked degeneration of chorionic epithelium. In both instances the chorionic epithelium has been deprived of much of its blood supply. We know that there is a circulating toxin in eclampsia. (We have made quantitative determinations of the tyramine in the blood of eclamptics, and we feel that other

TABLE I. SUMMARY: OBSTETRIC HISTORY: 93 PATIENTS, PREGNANT 362 TIMES, WITH RECURRENT ABORTION AND MISCARRIAGE

CONDITION OR RESULT	PREGNANCIES	PER CENT
Abortions	235	64.9
Miscarriages	69	19.1
Premature stillbirths	10	
Premature neonatal deaths	4	5.2
Term stillbirths	3	
Term neonatal deaths	2	
Live children		
Term	33	
Premature	6	10.8
Total pregnancies	362	100.0
Pregnancies with no living children	323	89.2
Pregnancies resulting in living children	39	10.8

TABLE II. THE RH FACTOR IN 93 CASES OF RECURRENT ABORTION AND MISCARRIAGE

RH FACTOR	PATIENTS	PER CENT
Present	76	81.7
Absent	17	18.3
Total	93	100.0

*Frequency of Rh Factor.*—In Table II it is revealed that the blood of 17, or 18.3 per cent, of the 93 patients did not contain the Rh factor. This is somewhat higher than the 15 per cent of women in the general population whose blood does not have the factor, and is higher than that which has been observed among women patients routinely seen by obstetricians and gynecologists of the Mayo Clinic.

TABLE III. THE RH FACTOR IN 34 CASES OF TRUE HABITUAL ABORTION (THREE OR MORE SPONTANEOUS ABORTIONS OR MISCARRIAGES WITH NO LIVING CHILDREN)

RH FACTOR	PATIENTS	PER CENT
Present	27	79.4
Absent	7	20.6
Total	34	100.0

If one corrects for the fact that the blood of two of the husbands of the seven women not having the factor similarly did not have the factor, then five, or 14.7 per cent, of the 34 women in this series could possibly be affected by the Rh factor. (These were the only husbands whose blood was tested in the group of women whose blood did not have the Rh factor.)

Also, the data in Table III point to some decrease in the occurrence of the Rh factor among women who have what is usually more rigidly defined as "true habitual abortion," as shown by the blood of 34 patients (in the series of 93) afflicted with this condition. The blood of seven of 34 patients, or 20.6 per cent, proved not to have the Rh factor. The blood of two of the husbands of the seven women who did not have this factor was tested and found not to contain the Rh factor. Thus, only five, or 14.7 per cent, of the 34 couples under consideration could have been involved by the Rh factor (woman not having the factor, husband having the factor). The percentage is slightly higher than that in the general population, since about 12 per cent of marriages involve women whose blood does not contain the factor with men whose blood does. However,



## THE Rh FACTOR IN ABORTION\*

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IN THE literature on the clinical importance of the Rh factor there are many intimations that this factor in the blood is a relatively common cause of abortion. However, only Schwartz and Levine and Javert discussed this possibility in detail. Levine noted that the blood of only one in nine women who had experienced two or more spontaneous abortions was Rh negative. Javert studied twelve cases of habitual abortion (number of pregnancies not stated) and found the blood of nine (75 per cent) of the women concerned to be Rh positive. He concluded that "unless additional evidence shows the contrary, early habitual abortions should not be attributed to (Rh factor) iso-immunization."

### Previous Work

In January, 1945, I reported results of a preliminary study carried out to determine whether or not the Rh factor seemed commonly involved in the etiology of recurrent abortion and miscarriage.† Twenty-five cases were collected over a period of two and a half years. In 22 (88 per cent) of these the blood contained the Rh factor, and in three (12 per cent) the blood did not contain this factor. Since the percentage of women whose blood did contain this factor was as large as that in the general population, it was tentatively concluded that etiologic influences other than the Rh factor had been in effect to produce these instances of repeated abortion.

### The Present Study

*Frequency of True Recurrent Abortion.*—The study to be reported now is an expanded one, similar in nature to the one just cited. It consists of a group of 93 women afflicted not only with recurrent abortion, but also with repeated miscarriage. Among these 93 women with recurrent abortion there were also a few instances of stillbirth and neonatal deaths. The patients represent, in so far as was possible, all such patients coming to the Mayo Clinic whose blood was tested for the Rh factor, who were pregnant and had such a history of recurrent abortion, or who were not pregnant but presented themselves with the primary or secondary complaint of repeated abortion or miscarriage. During the four years in which this series was collected there were approximately 75,000 women admitted to the clinic between the ages of 20 to 40 years. Hence, it will be seen that true recurrent abortion is not a very common condition. Table I represents the obstetric histories of these women as a group.

\*Read, by invitation, at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons at Hot Springs, Va., Sept. 5, 6 and 7, 1946.

†The terms "abortion" and "miscarriage" as used in this paper are based on the definitions given in Stander's text; that is, an abortion is a pregnancy which terminates before sixteen weeks' gestation; a miscarriage is a pregnancy which terminates between the sixteenth and twenty-eighth week of pregnancy.

resort was made to the tables of obstetric histories of 44 women whose blood did not contain the Rh factor and who bore infants with erythroblastosis, as published by Race, Taylor, Cappell, and McFarlane.

The data in Table VI point to no increase in the frequency of abortion in pregnancies after involvement by erythroblastosis fetalis. It may yet be too soon to determine this point. Javert wrote that iso-immunization by the Rh factor may increase the early termination of pregnancy by as much as 32 per cent.

TABLE VI. OBSTETRIC HISTORIES OF 44 WOMEN (178 PREGNANCIES) WITHOUT THE RH FACTOR WHO BORE ONE OR MORE INFANTS WITH ERYTHROBLASTOSIS\*

OUTCOME OF PREGNANCIES	PREGNANCIES BEFORE DIAGNOSIS OF ERYTHROBLASTOSIS FETALIS		PREGNANCIES AT WHICH DIAGNOSIS OF ERYTHRO- BLASTOSIS FETALIS WAS MADE	PREGNANCIES AFTER DIAGNOSIS OF ERYTHROBLASTOSIS FETALIS	
	NUMBER	PER CENT†	NUMBER	NUMBER	PER CENT‡
Living children	82	75.9	12	6	23.1
Stillbirths	11	10.2	3	2	7.7
Neonatal deaths	7	6.5	29	15	57.7
Abortions	5	4.6	0	0	
Miscarriages	3	2.8	0	3	11.5
Totals	108	100.0	45§	26	100.0

\*Modified from Race, R. R., Taylor, G. L., Cappell, D. F. and McFarlane, M. H.: Rh factor and erythroblastosis fetalis; investigation of 50 families, Brit. M. J. 2: 280-293 (Sept. 4), 1943.

†Of 108 pregnancies.

‡Of 26 pregnancies.

§One set of twins.

*Abortion Among Women Who Do and Do Not Have Rh Factor.*—Another way of appraising the influence of the Rh factor in abortion, especially in casual ordinary abortion as contrasted to recurrent abortion, is by review of the incidence of abortion in a sizable group of women who do not have the Rh factor, as compared with the incidence in a control group of randomly or consecutively selected women who do have the Rh factor.

In Table VII are presented such data. They confirm the assumption that so far as stillbirths and neonatal deaths are concerned, absence of the Rh

TABLE VII. RESULTS OF PREGNANCY AMONG 228 WOMEN WHO DID NOT HAVE RH FACTOR AND 228 WOMEN WHO DID HAVE RH FACTOR

PREGNANCIES AND RESULTS	RH FACTOR			
	ABSENT, WOMEN		PRESENT, WOMEN	
	NUMBER*	PER CENT†	NUMBER*	PER CENT‡
Living children	313	83.0	277	83.2
Ectopic pregnancies	4	1.1	3	0.9
Abortions, all	31	8.2	37	11.1
Miscarriages	5	1.3	11	3.3
Stillbirths	17	4.5	3	0.9
Neonatal deaths	7	1.9	2	0.6
Total pregnancies	377	100.0	333	100.0

\*Of pregnancies or conditions noted; not number of patients.

†Of 377 pregnancies.

‡Of 333 pregnancies.

there were only 93 cases in the total series, and we should hesitate to generalize on the basis of so small a series. Moreover, it must be emphasized that this series is concerned only with recurrent persistent abortions. It may be noteworthy to remark that no proved instance of erythroblastosis was noted in the histories of these 93 patients, nor at their subsequent delivery in the Section on Obstetrics and Gynecology of the Mayo Clinic. One case, in review, probably involved erythroblastosis, and the histories of two other patients are suggestive. Of course, many of these histories extend back well before 1940 and our exact knowledge of the Rh factor.

TABLE IV. PRESENCE OR ABSENCE OF RH FACTOR AMONG 25 PATIENTS WHO HAD ONE NORMAL LIVE BIRTH FOLLOWED BY A SERIES OF NONPRODUCTIVE PREGNANCIES, MISCARRIAGE, STILLBIRTH, ETC.

ONE LIVE BIRTH FOLLOWED BY	RH FACTOR, PATIENTS	
	PRESENT NUMBER	ABSENT NUMBER
Two nonproductive pregnancies	8	0
Three nonproductive pregnancies	5	2
Four nonproductive pregnancies	8	0
Five nonproductive pregnancies	2	0
Totals	23	2
Percentages	92	8

*Possible Effect of Rh Factor After One Normal Delivery.*—Table IV concerns a subgroup of the 93 patients who had recurrent abortion and miscarriage. This subgroup is composed of 25 patients who first had a normal living child and then were pregnant two or more times, each time nonproductively. Members of this group presented a type of obstetric history that could often, by reason of its sequence of events, theoretically be attributed to the action of incompatibilities of the Rh factor. It will be noted that the percentage of women who did not have the Rh factor is less than that observed in the general population.

*Frequency of Abortion, After Erythroblastosis Fetalis, in Women Affected by the Rh Factor.*—The problem of the Rh factor as it influences abortion can be viewed in a reverse light; namely, do women who are affected by the Rh factor to the point of delivering erythroblastotic fetuses experience abortion with any greater frequency than women not thus affected?

In Table V is revealed our experience with this type of patient in the two years prior to the time of this report. The table shows no evidence of abortion or early miscarriage in this very small series of 13 patients. Only seven pregnancies in Table V are those subsequent to the birth of infants who had erythroblastosis. Because these data are far too small to be at all conclusive,

TABLE V. SUMMARY: OBSTETRIC HISTORIES: 13 PATIENTS DELIVERED OF 20 ERYTHROBLASTOTIC FETUSES IN 43 PREGNANCIES\*

TERMINATION OF PREGNANCY AT	NUMBER OF PREGNANCIES
Under six months' gestation	0
Six to eight months' gestation	6
Eight months' gestation or more	37
Total pregnancies	43

\*Seven infants were stillborn or died in a few minutes, and their condition was assigned a definite or presumptive diagnosis of "erythroblastosis fetalis."

among women who do not possess the Rh factor than among those who do. When recurrent abortion and miscarriage are considered, however, the number of women in a group of 93 whose blood did not contain the Rh factor was somewhat higher, comparatively, than would be true in the general population. Conversely, on the basis of the data analyzed, there seems to be no striking increase in the frequency of occurrence of abortion or miscarriage after maternal involvement by the Rh factor as evidenced by the occurrence of erythroblastosis fetalis. On the other hand, there is a striking increase in the casualties of late pregnancy among women whose blood does not contain the Rh factor. Data concerning a small series of 25 women who gave birth to a normal child and then began to experience abortions and miscarriages were analyzed. In this series there were fewer women whose blood did not contain the Rh factor than are found, comparatively speaking, in the general population.

The Rh factor possibly has been overemphasized as a cause of abortion and miscarriage at the expense of more common causes, such as dysfunction of the ovaries, pituitary body, thyroid glands, and possibly the testes of the husband. A woman subject to habitual abortion whose blood does not contain the Rh factor deserves a chance to attempt another pregnancy under the more nearly ideal physiologic environment than proper therapy may provide.

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### Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—Whenever a discovery is made in the practice of medicine, whether it be diagnostic or therapeutic, we can be assured that false as well as true assertions will prevail about its action until sufficient time will have elapsed for critical evaluation of the claims made concerning its action by the earlier workers in the field. Dr. Hunt has tested out the claim that the Rh factor is an important cause in the production of casual and habitual abortion and found it wanting. The data he presents show without doubt that in this series there is no evidence that the Rh factor had any important part to play in the causation of abortion. The weakness of a study such as this lies in the relatively small number of cases which, as Dr. Hunt rightly points out, renders the statistical value of only relative importance. However, because it is difficult now and has been more difficult because of war conditions and because of the scarcity of the antigen in the early years of the discovery of the Rh factor, it is necessary for various clinics to supply information on their experience which, when pooled with that of other clinics, will give us the answer we are seeking.

Our experience with habitual and casual abortion has led us to the belief that in most cases the cause of the abortion was due to anatomic or endocrinologic defects which when corrected resulted in a very favorable effect on the tendency to abort. If the Rh factor

factor is a definite hazard, because the incidence of these two casualties of pregnancy was 6.4 per cent among women who did not have the factor, whereas in the control series of women who did have this factor, the incidence was only 1.5 per cent. There is no similar evidence that absence of the Rh factor is an important cause in the production of *early* casualty of pregnancy. For neither abortion nor miscarriage was the rate of occurrence greater among those women who did not have the Rh factor than among those who did. In fact, in these two series, each composed of 228 women, there were actually fewer abortions and miscarriages (9.5 per cent) among women who did not have the factor than among women who did have the factor (14.4 per cent). Hence, we must hold in abeyance any opinion that the Rh factor is an important cause of abortions and miscarriages, as these two casualties of pregnancy ordinarily are encountered. If absence of the Rh factor has a part in the causation of abortion, it is overshadowed, so to speak, by other causes, and is not apparent statistically. As I have suggested previously herein, the situation is somewhat different in respect to persistent abortion.

### Comment

If an abortion is caused by the results of iso-immunization by the Rh factor, it would seem logical to expect to find anti-Rh agglutinins in the mother's blood early in pregnancy, in the blood of at least some of the women tested, and in a significant titer. Reports of such findings have not yet been published. In the few cases in which we have carried out such tests to date, anti-Rh agglutinins have not been found. Vaux and Rakoff have reported that the results of such tests of the blood of two women subject to habitual abortion were negative. The Rh factor has been demonstrated in the fetal blood as early as the fourth month of gestation by Börnstein and Israel, and also by Kariher and Spindler. It may be that time and further study will justly implicate the Rh factor in the cause of spontaneous interruptions of early pregnancy in some cases. However, the facts that the blood of a woman subject to habitual abortion does not contain the Rh factor, and that such a woman is married to a husband whose blood does contain the factor, should in no way call forth the opinion that the prognosis for her pregnancy is poor. She is still entitled to the usual investigation and therapy that are extended to any group of relatively infertile patients, and her chances for successful termination of pregnancy are worth an effort on the part of her obstetrician.

The Rh factor is carried chiefly in the erythrocytes. The total fetal cell volume early in pregnancy must be small. In other words, the volume of the Rh antigen is too small to be able to influence the mother until at least mid-pregnancy. Theoretically, this may explain the discrepancy noted in Table VII between the effect exerted by the Rh factor on casualties of *late* pregnancy compared with those of *early* pregnancy.

### Conclusions

Casual or ordinary abortion seems uninfluenced by the mechanism of the Rh factor. The incidence of stillbirth and neonatal deaths, however, is higher

## RED DEGENERATION OF UTERINE MYOMAS\*

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RED, or carneous, degeneration of uterine myomas was first described by Gebhard<sup>1</sup> in 1899. Probably this type of degeneration was known before, but an accurate description is lost in the early classification of myomas as either "soft" or "hard" without much separation of specific types within that general classification.

In 1903 Fairbairn<sup>2</sup> of England reported 19 of these tumors and presented a complete description of their clinical characteristics and pathology. In 1910 a valuable contribution was made by Murray,<sup>3</sup> pointing out the possible hemolyzing effect of the lipoids in red myomas to explain their color. In 1913 a very specific pathologic classification was made by Smith and Shaw.<sup>4</sup> They divided these tumors into two groups, those in which thromboses were found in the vessels within the tumor, and a smaller group in which the coloration was looked upon as being the result of spontaneous hemolysis and diffusion. Haultain<sup>5</sup> also, in an article for an English system of gynecology, theorized about the type of vascular accident which causes this degeneration.

Since the extensive English publications in the early part of the century occasional reports<sup>6, 7</sup> of red myomas, especially as related to pregnancy, appear in the literature, but for the most part the ideas expressed are not much different from those found in earlier publications. The opinion has been frequently recorded that in pregnancy there may be a special toxin to explain the hemolysis. Finally, some individual tumors of this variety have been looked upon as true angiomas.

It would seem that, in general, this degeneration, though unique as degenerations in myomas go, has been made unnecessarily complicated. The purpose of this paper, though none of the ideas are new, is to try to simplify some of the aspects of red degeneration and to present pathologic specimens.

As indicated above, many ideas as to the etiology of this condition have been expressed. In general, one is impressed by the general failure to apply to red myomas the principles of Sampson's<sup>8</sup> work done in 1912 on the blood vessels of the myomatous uterus. In considering the mechanics of this subject, it seems important to talk definitely about arteries and veins of the myoma and not in general about "blood vessels" as is so commonly done. Sampson's injection work, done with gelatin and repeated during the last few years with synthetic liquid latex,<sup>9</sup> makes it plain that the vessels within a myoma inject as arteries, and that veins are concentrated about the periphery of the myoma and, although they may be large, they penetrate the tumor very little or not at all.

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

had been an important contributing factor we should have failed to get the response which we did get when we corrected these anatomic and endocrine factors in a larger percentage of cases.

I should like to emphasize what Dr. Hunt has pointed out, that it is highly improbable that enough of the Rh factor would be likely to get from the fetal to the maternal circulation in the early stages of pregnancy to have a serious significance in the causation of early abortion, since the factor is carried by the red cells.

In the later months, in normal as well as pathologic cases, the vascular accidents in the placenta, infarct formation, and degenerative changes may well lend themselves to destruction of fetal red cells and absorption by the mother of the antigen, or the transfer of whole cells into the maternal blood stream. This would result possibly in producing circumstances that would lead to premature labor or erythroblastosis, but not habitual abortion.

We have analyzed routinely 615 cases with only 38, or 6.1 per cent, Rh negative. If we had had 1,000 cases the figures might be more comparable to those found in the general population.

RH FACTOR DETERMINATIONS—615 CASES  
(FEBRUARY 22, 1946, TO AUGUST 31, 1946)

	NUMBER	PER CENT
1. Rh-negative women	38	6.1
2. Rh-negative women with Rh-positive husbands	16	
3. Rh-negative women who came to the clinic for abortion or miscarriage	1	
4. Abortions or miscarriages which were uncomplicated by Rh considerations. (Taken from a survey of 100 Rh-positive multiparas)	25	25.0

RH-NEGATIVE WOMEN WITH RH-POSITIVE HUSBANDS—16 CASES

	NUMBER	PER CENT
1. Rh-negative women with Rh-positive husbands who have a history of habitual abortions or miscarriages	5	31.2
2. Rh-negative women with Rh-positive husbands uncomplicated by abortions or miscarriages:		
A. Primiparas (undelivered*)	4	25.0
B. Multiparas	7	43.7

\*It is difficult to evaluate the primiparas since we do not know the prognosis of their gestation, but they had passed the fourth month of pregnancy.

It would seem, therefore, that our figures corroborate the findings of Dr. Hunt, although too small in number to be statistically significant. In the light of these findings it would seem proper to encourage Rh-negative women with Rh-positive husbands to become pregnant in the belief that they have not much more than the ordinary risk to run from abortion, and that we should focus our attention on the management of other causes of abortion in such cases that present themselves with a history of habitual or recurrent abortions.

periphery of the tumor where the concentration of veins exists. Venous obstruction as postulated by Haultain, whether from simple pressure, peripheral thrombosis as seen in some specimens (Figs. 2 and 3), or mechanical injury as seen in one (Fig. 4) appears as a possible cause of the pathologic picture. Blood is pumped into the tumor and cannot get out. The thin-walled arteries of the



Fig. 2.—Large soft red tumor with peripheral thrombus. Patient had pain, fever, and leucocytosis.



Fig. 3.—Smaller red myoma. No symptoms. Peripheral thrombosis.



The usual myoma is fed by multiple branches from a vascular are in the uterus, although one of the vessels supplying it may be larger than the others. In the beginning the blood supply always looks adequate for nourishment of the tumor although, as is well known, myomas vary a great deal in vascularity. Vessels within the tumor, although arteries, are usually thin walled. Anemic infarction of a myoma is practically unknown except as a gradual process manifest in the ordinary hyaline and cystic degeneration of these tumors. These ordinary degenerations indicate a disturbance of greater or lesser degree in the arterial side of the circulation. The tumor lacks for nourishment, therefore muscle cells and bundles break down and may even liquefy. The usual explanation offered for the arterial changes is that the tumor grows or is extruded away from its primary focus faster than proliferation of arteries can follow. Certain it is that the centers of tumors or those points in others farthest from the source of blood supply break down first.



Fig. 1.—Partial and patchy red degeneration of a myoma

From the clinical behavior of the red myoma, the acute symptoms associated with some, and its gross pathologic appearance, it is evident that this degeneration is a vascular accident, viz., hemorrhage into its substance. Two possibilities exist. The first is primary rupture of vessels within the tumor which are arteries. It would seem that in the full-blown example many ruptures without discernible cause would have to occur at the same time to explain the picture. Although partial or patchy red coloration (Fig. 1) occurs and could be explained on this basis, there is still necessary an explanation for the apparent sudden transformation of a whole myoma nodule, sometimes of a large size, into a tense red tumor. More reasonable, it seems, to look for trouble about the

Although this is believed to be the mechanics of the usual red degeneration, it is apparently certain that a "healthy" myoma will never undergo typical red degeneration, even though hemorrhage occurs within its substance. It would seem that the right degree of hyaline conditioning of the tumor before the vascular accident occurs, is necessary before red blood cells are laked and diffusion of pigment takes place. It is not possible at the present time to refute the idea of Murray<sup>3</sup> that lipoids in the tumor produce the laking, but in many of the tumors studied ordinary fat stains revealed no fat. It is not understood why the ordinary amine cell products of degeneration already present in the myoma which is to be a red one, could not break down red blood cells. On occasion at operation blood has been withdrawn and injected into myomas. The ordinary hard myoma shows no staining except immediately about the needle wound. The softer the myoma, the more diffusion occurs. This experiment is comparable to that of Murray, who immersed pieces of myomas in a hemoglobin solution. Suffice it to say in no myoma has a typical red degeneration been produced. This is understandable probably because a great many small areas of extravasation are present when the accident comes about naturally. It seems possible that the precursor to red degeneration—proper hyalinization—may in addition to changes in chemistry and texture which allow for laking and diffusion, respectively, also make arterial rupture easier when venous obstruction occurs because of loss of firm supporting substance about the vessel walls. Previous hyalinization may govern to some extent the degree of red change. Certainly, firm myomas are frequently seen with large or small hemorrhage into them without general diffuse red transformation.

Much of the complexity of information relating to red myomas arises from the great variety of gross and microscopic features which these tumors present. The point should be made that characteristics of these tumors vary with the time they are seen as related to the vascular accident. If studied early enough it is believed extravasated red blood cells could be found in all of them. Later, such a finding naturally would not exist and, as is well known, does not. Thrombi in the arteries of the tumor itself exist, but if looked upon as due to natural stasis and not as the cause of the degeneration, are to be found only in red myomas of older vintage. Generally speaking, this seems to be true. Thrombi in the veins of the periphery, however, if present at all, are there in recently infarcted tumors, but, as stated above, are not the sole cause of venous obstruction in these tumors. Perhaps even the much discussed presence or absence of demonstrable fat depends on the recentness of the infarction. None of the occasionally reported intrinsic vascular changes consisting of fibrin deposits or actual endarteritis have been seen in the tumors studied. It is surmised that even if occlusive vessel changes are commonly seen that, being arteries, the changes would pertain to the pre-existing hyaline degeneration rather than to the vascular accident which caused the red degeneration.

The point has been made that *typical* red degeneration is seldom seen in twisted pedunculated tumors of connective tissue or smooth muscle, the hemor-

myoma are ruptured at many points and extravasation of red blood cells occurs (Fig. 5). Such a concept readily explains the rapid swelling of the myoma which has suffered this accident, its tenseness, edema, and the uniform coloration which typical ones present.



Fig. 4.—Red myoma 9 cm. in diameter when removed two months after an attempted abortion. Peripheral injury.



Fig. 5.—A frequent finding in early red degeneration. Thin-walled arteries are engorged with multiple rupture and extravasation of red blood cells.

supply as well as interference with lymphatics about which latter subject little is known as related to myoma. The color of the older dry tumor is likely to be dull brown to slate color, and in some scattered calcification is present. One experience with a large solitary myoma which suffered the accident of red degeneration in the puerperium and was removed by myomectomy several months later, showed a shrunken slate-colored tumor quite dry over the surface and most particularly adherent in its uterine bed. The loose areolar tissue about the myoma was replaced with relatively avascular scar tissue.

The frequency of symptomatic red degeneration in myomas is not great. An incidence of 7 or 8 per cent of all myomas has been handed down as an authentic figure with most occurring, of course, in connection with pregnancy. There is no doubt that when looked for faithfully by the prompt opening of all myomas removed, some degree of hemorrhage and coloration is fairly frequent, even in the nonpregnant uterus. Many tender nodules which are never removed during pregnancy or the puerperium undoubtedly are victims of this change. In our cases, whether pregnant or not, good symptom-producing red myomas have been less than 1 per cent. In these days when myomas in general do not become so large before operation as they used to, it would seem an over-all incidence in pathologic material of 5 per cent is high enough.

With larger myomas which have suffered this accident some patients develop fever and leucocytosis. In the nonpregnant woman, it is doubtful whether the diagnosis of red degeneration can very often be made in small myomas even by reviewing the patient's history after their discovery. Many good small ones are seen which give no symptoms, not being pushed up under the abdominal wall as in pregnancy. All tumors diagnosed before operation in the nonpregnant uterus from signs and symptoms were 10 cm. or more in diameter at the time they were causing trouble. Problems in differential diagnosis occasionally arise. The most common is to determine whether the patient may be suffering from salpingitis rather than from infarction of a myoma. When fever occurs with one of these tumors during the puerperium or the course of an abortion in a myomatous uterus one is faced with the problem of deciding whether puerperal infection is present or not. Rightly placed on the proper aspect of a pregnant uterus, a small red myoma may quite successfully simulate appendicitis.

Since these tumors rarely become infected or completely break down or liquefy, the treatment of them when diagnosis is certain is obvious. Left alone and treated expectantly, especially important in the pregnant uterus, the symptoms quiet down and the tumor shrinks up without too frequent complications. The patient, however, often becomes rather irked at the long-continued discomfort. In the nonpregnant woman, the patient may be treated medically through the acute phases of infarction and surgical treatment carried out with greater ease at a later date. Again it is to be said that such treatment is to be followed only when there is little uncertainty about the diagnosis. One such supposed myoma treated expectantly turned out to be hemorrhage into a granulosa cell tumor. Pedunculated myomas perhaps should not be handled in this way because of the likelihood of twist. Although the process within the

rhage and coloration being more focal in most twisted tumors and lacking the diffuse tinting characteristic of red degeneration (Fig. 6). It is not believed that there is any discrepancy between twisting of a pedunculated tumor and red degeneration, if conditions are similar. The degree of twist should be enough to shut off veins and not arteries, and most particularly the right hyaline conditioning of the tumor before the accident of the twist is necessary if the coloration is to be diffuse.



Fig. 6.—Twisted pedunculated myoma. Somewhat more irregular and patchy discoloration than in conventional red degeneration.

After the accident of red degeneration has occurred in a myoma and the stages of acute swelling and extravasation are over, the recovery of the tissue is the same as the recovery from hemorrhage in any structure. Gradually the pain and tenderness of the tumor, undoubtedly caused by the tension within, quiet down, the constitutional signs disappear as the tumor becomes smaller. From observation in a limited number of instances it is believed that a myoma which has suffered the accident of red degeneration may ultimately be even smaller than the original tumor. Infection may occur in these tumors, but it is very rare and usually connected with heavy inoculation from pregnancy or abortion (Fig. 4). Strangely enough, sufficient circulation usually remains or is restored so that complete breakdown and liquefaction of the tumor are rare. The tissues go through the same processes that any black eye or other bruise goes through, and only rarely are any late toxic signs or symptoms discernible in the patient. A curious dryness of some older tumors of this character is common. This is interpreted on the basis of diminution in arterial blood

without fever and with or without signs of threatened interruption of pregnancy, presents no indication per se for myomeetomy once the correct diagnosis is made.

I have observed that the irritability of the uterus appears to be controlled satisfactorily within twenty-four to forty-eight hours by the intravenous or intramuscular injection of lutein (Hynson and Westcott) even after opiates and rest in bed have failed. When dealing with a patient whose obstetric future is not bright by reason of advanced age or simply because of multiple fibroids, every means should be taken to avoid operation. Myomeetomy, of course, can be done without interrupting pregnancy probably safer in the first trimester, though the danger is real and the operation is seldom necessary.

In reviewing some of the specimens which have been removed at cesarean section at the Hartford Hospital, I was impressed with the fact that sometimes no history of a preceding attack could be elicited in a case which presented typical red degeneration. I was also impressed with the innocuous appearance of hyalin degeneration which a fibroid can assume within three or four months after a severe attack of red degeneration which had been sufficient to threaten interruption for many weeks. The appearance of the tumor whether red, brown, slaty grey, yellow, or even with calcification depends on the time following the vascular accident.

tumor is looked upon as being the same, twisting of the tumor may be associated with greater shock and pain and the arterial supply to the tumor be more interfered with leading to ultimate complete necrosis of tissue.

### Summary

Red degeneration of uterine myomas is considered in the light of what is known of the blood vessels of the myoma. It seems clear that red degeneration is a hemorrhagic infarction of a previously hyalinized myoma. Venous obstruction which has to be at the periphery of the tumor is put forth as the vascular accident which best explains this pathologic entity.

It is emphasized that the time the tumor is seen as related to the vascular accident governs the specific pathologic findings.

In the nonpregnant uterus red myomas are usually 10 cm. or more in diameter before there are symptoms or signs enough to make their preoperative diagnosis very certain.

Conservative medical treatment of the acute phases of red degeneration is feasible when the diagnosis is clear and in pregnancy highly desirable.

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### Discussion

DR. JAMES R. MILLER, Hartford, Conn.—Dr. Faulkner has reviewed one of the most interesting accidents which occur in the life history of uterine myomas. From his work and from that of Dr. Sampson, it is clear (1) that the blood vessels of myomas are arteries and arterioles and most probably there is a bed of capillaries which empties into veins that are found only at the periphery; (2) that a single nutrient artery is often insufficient to nourish a myoma; and (3) that there is apparently no communication between capillaries and lymphatics in a myoma.

Vascular accidents involving leiomyomas of the intestine give rise to profuse and often fatal hemorrhage, and it may be that they too are supplied only with vessels of the arterial type. They lack the firm capsule which is found in the uterine myoma, and one can readily understand why the picture of infarction or red degeneration is not found, but rather one of uncontrolled and unconfined hemorrhage.

In the minds of some obstetricians who are not familiar with the usual benign course of red degeneration, there may still linger an idea that the painful tumor must be excised lest it grow larger later on in pregnancy, even though the risk of interrupting pregnancy is great. More than one myoma may successively undergo red degeneration as in a patient who is now under my care.

It must be clear by now that a myoma, which presents a sudden painful swelling during pregnancy with leucocytosis and perhaps some elevation of the blood sedimentation rate but

have some effect upon endometriosis,<sup>16</sup> and we have had no opportunity to use androgen preoperatively for adenomyoma or adenomyosis.

Our method of administration has consisted mostly of 150 to 225 mg. of testosterone propionate in oil injected intramuscularly over a period of two to three weeks, followed by 10 mg. daily of methyl testosterone orally for variable periods up to three or more years in three patients, rather than the much less expensive but less controllable pellet implant method.<sup>17</sup> Other than slight virilism and occasional acne, reactions have been negligible.

### Case Reports

*Diagnosis.*—Negative effect upon polycystic ovaries and inflammatory residues was mentioned. In addition to the two cases below, most of the following 17 cases may also be taken as diagnostic.

CASE 1.—(C. T.), single, 36 years of age, abdominal pain after bowel movement for two years, dysuria (hematuria  $\times 1$ ) for four weeks; posterior uterus, stenotic cervix, myoma, cul-de-sac endometriosis. Treatment: dysuria relieved, cul-de-sac insensitive, bowel pain persists. Suspected large bowel endometriosis disproved via testosterone proved to be proctitis.

CASE 2.—(R. U.), married, 23 years old, infertile, acquired right lower quadrant pain with menses, not relieved by appendectomy; posterior uterus; husband sterile. Three years later, acute peritonitis, cause? Painful menses, large left ovarian cyst, improved with treatment, but operation preferred; pelvic endometriosis and chocolate cyst confirmed, latter removed. Recurrent pain relieved by testosterone.

CASE 3.—*Conservative Treatment.*—Reported in 1943, a case of seven-year sterility, excision of right chocolate cyst, uterine suspension, delivery. Has taken 10 mg. methyl testosterone daily since October, 1942, with no increase in left ovarian endometrioma and no unfavorable manifestations except slight hirsutism.

CASE 4.—Also reported in 1943; first operation, removal of large ruptured right ovarian endometrial cyst; removal of extremely large left ovarian chocolate cyst refused, but opened and drained at second operation for intestinal obstruction. Has taken 10 mg. or more of methyl testosterone daily since May, 1942, with incomplete but marked regression of tumor, relief of pain, and semiobstructive symptoms, and only slight voice change, hirsutism, and vulvar hypertrophy.

CASE 5.—(R. S. C.), married, 36 years of age, has one child; recent menstrual pain, nausea, distention; appendectomy in 1940, adnexa found "O.K." Unrelieved by Elliott vaginal heat; operation: right salpingo-oophorectomy for "tubo-ovarian abscess." Marked regression of secondary large left ovarian endometrioma with relief of menstrual pain, diarrhea, and other intestinal symptoms effected after only three weeks of intensive treatment. This patient was treated intermittently from May 14, 1943, to May 2, 1946, with incomplete regression of ovarian tumor, persistent, fixed, large, posterior uterus, and nodular uterosacral ligaments, but with subjective relief and no troublesome reaction.

CASE 6.—(M. T. S.), married, 28 years old, has two children; polymenorrhea with acquired left lower quadrant pain; posterior uterus, cul-de-sac endometriosis. Symptoms required 20 mg. daily orally two weeks per month intermittently for thirty months, followed by pregnancy, recently delivered.



## CONSERVATIVE TREATMENT AND THERAPEUTIC TEST FOR ENDOMETRIOSIS BY ANDROGENS\*

JOHN COOKE HIRST, M.D., F.A.C.S., PHILADELPHIA, PA.

FROM observations beginning in 1942,<sup>1</sup> we can state that androgen will not cure "external" endometriosis, exerts relatively little regressive effect upon hard infiltrates or fused masses as compared to cystic endometriomas, and, apart from the menopausal period, has but temporary action. Also, it may induce arrhenomimetic symptoms, which are always objectionable, possibly serious and permanent,<sup>2</sup> but, except from heavy prolonged dosage, are not inevitable and may be mild.

Notwithstanding the above, aside from relation to endometriosis, androgen has both negative and positive values. Unlike estrogen, it is neither experimentally<sup>3</sup> nor clinically fibromatogenic or carcinomatogenic,<sup>3a, 4</sup> but rather antigenic in these respects, particularly versus inception of mammary cancer.<sup>5</sup> It has positive value in spasmodic dysmenorrhea and mastalgia, less value in premenstrual tension<sup>6</sup> and "functional uterine bleeding," although not comparable to estrogen<sup>2, 8</sup> for the latter condition. Androgen also exhibits a "tonic" effect approaching euphoria notably at the menopause, when other favorable action may be prominent.<sup>9, 10</sup>

In relation to endometriosis, androgen has also both negative and positive values. Unlike estrogen, it will not reactivate the disease after the menopause,<sup>11, 12</sup> and, according to two of our cases, will not cause regression of cystic ovaries associated with peri-oophoritis and excessive bleeding. Although androgen has been used for acute pelvic inflammatory disease to suppress menstruation, we have not seen regression of inflammatory residues, and therefore suggest the last two negative observations as diagnostic possibilities.

The positive values of androgen, particularly in rapid reduction of pain, tenderness, and swelling of grossly cystic ovarian endometriomas, will be described in 19 brief case reports under diagnostic, therapeutic, preoperative, and postoperative headings, not including a larger number of early nodular cul-de-sac endometriosis with minor symptoms.

Contrary to original intention, only inconclusive haphazard endometrial biopsies and vaginal smears were obtained and no hormonal assays<sup>13, 14</sup> so that nothing new can be presented as to etiology of the disease or biologic action of androgen. However, the rapidity of effect suggests a direct antagonism of androgen versus estrogen, in addition to known reduction of urinary gonadotropic hormone excretion, as indicated in two previous reports.<sup>1, 15</sup>

We have had no experience with the sterol desoxycorticosterone acetate, and no conclusive effect with progestin, each of which should theoretically

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5, 1946.

CASE 17.—(S. M. W.), married, 39 years old, one child, eleven years; acquired menstrual backache, pain right lower quadrant, prolonged menses; external tubal and cul-de-sac endometriosis; supravaginal hysterectomy, bilateral salpingo-oophorectomy. Endometriosis reactivated by estinyl, regressed with testosterone.

CASE 18.—(S. D. G.), married, 30 years, infertile; stenotic cervix, bilateral ovarian chocolate cysts, myomas, diffuse pelvic endometriosis. Operation: curettage, Rubin test, myomeetomy, oophorectomy, ovarian resection. Testosterone used to inhibit disease. No pregnancy.

CASE 19.—(N. W. D.), married, 41 years, acquired menstrual pain, many vague symptoms; relaxed vaginal outlet, cervicitis, prolapse, myomas, bilateral ovarian chocolate cysts, diffuse endometriosis. Operation: repair, total internal genital extirpation. Early postoperative testosterone immediately transformed this psychoneurotic woman to normal, with extraordinarily rapid regression of low pelvic endometriosis.

We have utilized testosterone after radical operations with great advantage in two similar additional cases, and feel that it should be regularly so used.

### Comment

Although androgen will help, there is obviously urgent need for endocrinologic research in a prevalent<sup>25</sup> and serious disease which may occur as early as 13 years of age,<sup>26</sup> and for which there is not yet ideal hormone control or reasonable conservative surgery.<sup>27</sup>

### Summary and Conclusions

Clinical experience with numerous early and 19 listed advanced cases of "external" endometriosis, several of which have been treated up to four years, indicates certain usefulness of androgen therapy.

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CASE 7.—(A. D. B.), married, 35 years of age, childless; acquired menstrual pain (right labial, ischio-rectal, sciatic); cervical stenosis, right ovarian endometriosis. Testosterone (Sept. 27, 1943 to Nov. 19, 1944) relieved pain, regressed tumor, shrunk breasts slightly and uterus considerably, atrophied endometrium, reduced flow, increased libido, produced voice huskiness, no effect on normally large clitoris. Last menstrual period occurred Oct. 21, 1944 (scant under treatment<sup>18</sup>). Delivered July 27, 1945, less recurrent pain since.

CASE 8.—(M. H. S.), single, 25 years of age, acquired right and left lower quadrant menstrual pain, nausea, vomiting, diarrhea; appendectomy and left salpingo-oophorectomy, ruptured endometrial cyst. (January, 1943); uterus large, adnexal endometriosis. Uterus smaller, menses improved with testosterone, voice slightly hoarse.

CASE 9.—(M. E. C.), married, 27 years old, infertility, poly-hypermenorrhea with pain; right salpingo-cystoophorectomy and appendectomy for 5 cm. endometrioma, resection of left ovary; left adnexal endometriosis; regression uterus; tumor, normal flow, persistent pain (habitual) after three months' treatment.

CASE 10.—(H. P. R.), married, 34 years of age, one child, acquired menorrhagia with pain in right lower quadrant; cervicitis. Cornual myoma, and right adnexal endometriosis, cervical coagulation; methyl testosterone Oct. 17, 1944 to April 13, 1945, menses improved, adnexal tumor reduced.

CASE 11.—(F. L. M.), married, 26 years of age, two children, acquired right lower quadrant pain near menses; large uterus, uterosacral and adnexal endometriosis; with two months of intensive treatment, menses were scant, with little pain, some virilism and acne, gained weight. Examination: pelvis almost negative.

CASE 12.—(S. H. N.), married, 31 years of age, infertile, acquired abdominal and back pain, bilateral adnexal endometriosis, especially right; four months treatment, no pain with menses, right ovarian mass smaller, reaction, urticaria.

CASE 13.—(D. R. N.), single, 19 years old (courtesy Dr. Irving Uram), acquired right ureteral distribution menstrual pain, cystoscopic diagnosis; slight hydronephrosis; right simple ovarian cyst not affected by testosterone which relieved pain, therefore removed and ureteral endometrial implant diagnosed.<sup>19-21</sup> Testosterone discontinued, pain recurred, radical operation elected.

CASE 14.—(E. M. P.), married, 24 years of age, one abortion, acquired menstrual pain, metrorrhagia; erosion, extremely tender posterior uterus (not replaceable); large cystic right ovary, large left vaginal fornix, endometrial mass, abnormal bleeding ceased, uterus and tumors smaller under treatment.

CASE 15.—*Preoperative*: (I. L. W.), married, 51 years, three children, last eighteen years; three weeks' treatment failed to regress dense pelvic endometriosis sufficiently to permit total hysterectomy for uterine myomas. However, we believed preoperative treatment to be useful.<sup>22</sup>

CASE 16.—*Postoperative*: (R. D. H.), married, 34 years, infertile, menorrhagia, menstrual cramps, myomas, extensive endometriosis, including vagina, anus, rectum,<sup>23</sup> but *not* ovaries. Pelvic endometriosis did not regress after supravaginal hysterectomy<sup>24</sup> until after testosterone therapy, which has not reduced the hard vaginal infiltration appreciably, from Oct. 15, 1941 to July 22, 1946. Reaction, occasional hoarseness.

## THE SECOND STAGE OF LABOR; INTERNAL ROTATION\*

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(From the Kansas University Hospitals)

INTERNAL rotation has long been the most interesting feature of the mechanism of labor. This interest has been partly due to the fact that the etiology is unknown. A great difference of opinion has also existed with reference to the significance of failure of rotation.

This present study has two objectives. It was thought that if we could learn more exactly the time at which internal rotation occurred and study carefully the results of failure of rotation, we might possibly arrive at a more definite knowledge of why internal rotation takes place. Or, failing that, we might learn how better to manage the unrotated head.

For the past several years, we have tried to improve our labor records by noting carefully the direction of the sagittal suture and the exact presenting point with reference to the two fontanels at each successive examination during labor. Vaginal examinations have deliberately been made as frequently as necessary when exact information on these points was not available by rectal examination. During the second stage particularly, the direction of the sagittal suture was noted frequently. It was our impression that internal rotation usually takes place while the head is descending to the pelvic floor. We, therefore, made it a particularly urgent necessity to know whether this was true. As a result of having made these careful records on some 2,900 primiparas and some 2,500 multiparas, we can now say that internal rotation is complete at the time the head reaches the pelvic floor in approximately two-thirds of all patients (hereafter referred to as early rotation). In something less than 30 per cent, internal rotation is completed very shortly after the head reaches the pelvic floor. The length of time varies from as little as one uterine contraction in a multipara to as many as ten or twelve contractions in some primiparas.† In something over 4 per cent of all patients, rotation to the anterior does not take place. In a portion of these, rotation posteriorly to the hollow of the sacrum occurs. In another portion, partial rotation anteriorly is observed (as from an obliquely posterior position to an obliquely anterior position). The largest fraction of this 4 per cent, however, is made up of those patients in whom no internal rotation occurs. Two and six-tenths per cent of all primiparas and 1.4 per cent of all multiparas fall into this latter group. It should be pointed out that not all of these patients are truly "persistent" occiput anterior or "persistent" occiput posterior. Of 100 such primiparas, 25 delivered spontaneously

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

	Primiparas	Multiparas
†Early	1827	1734
Late - soon -	347 - ave. 6.6 mins.	353 - ave. 3.3 mins
Late - delayed (?) -	564 - ave. 42.0 mins	311 - ave. 17.5 mins
Late - 3 groups -	143	100

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500 N. 20TH ST.

### Discussion

DR. EMIL NOVAK, Baltimore, Md.—There are some who believe that the endocrines play some part in the etiology of endometriosis, but this has never been established. All will agree, however, that endometriosis whether occurring normal within the uterine cavity or growing ectopically, as it does in pelvic endometriosis, is under the influence of the ovarian hormones. On the basis of our experience with the use of the androgenic hormone in the treatment of functional bleeding, it seems likely that this hormone does have some degree of anti-estrogenic effect upon the endometrium, presumably mediated through the pituitary, and always very temporary in its effects.

Endometriosis is not characteristically associated with excessive menstruation, but in some cases a dysfunctional factor co-exists, with functional bleeding in which testosterone may be helpful. However, I gather that Dr. Hirst advocates its use as a palliative for the dysmenorrhea so often seen with endometriosis. This is likely to be severe chiefly in those cases in which the endometriosis is fairly extensive, as with a unilateral or bilateral endometrial cyst, with or without involvement of the uterosacral area. In such cases surgery is certainly to be preferred to the continued use of testosterone, month after month and perhaps year after year. In the more moderate degrees, pain may not be severe or for that matter may be absent altogether. Moreover, such cases cannot be diagnosed before operation, although I have noted an unfortunate tendency to make a presumptive diagnosis of endometriosis simply because a patient has otherwise unexplainable dysmenorrhea.

fact that, in this series, early rotation was considerably more common with good labor pains than it was with poor labor pains.\* We thus find that multiparas with good labor pains will have early rotation in 72 per cent of all cases. Primiparas with poor labor pains, on the other hand, will have early rotation in only 58 per cent of all cases. Failure of internal rotation similarly occurs in only 1.2 per cent of multiparas with good pains, and in this series was judged to have failed in 5.6 per cent of primiparas with poor pains.

Whereas the above findings do not definitely establish the etiology of internal rotation, it seems that we can very definitely state that parity and the character of the labor pains are definite factors in this process.

### Significance of Late Rotation

As previously stated, the vast majority of all heads unrotated at the time the pelvic floor is reached will rotate quite promptly thereafter. In multiparas particularly, this rotation takes place during the next one or two uterine contractions. In primiparas, three to five such uterine contractions are usually necessary. In these groups of patients, this amount of delay in rotation is not evidenced in the complete pelvic floor phase of the second stage. There seems to be sufficient distention while rotation is taking place that the whole pelvic floor phase is accomplished just as quickly as though the head had been completely rotated at the time the pelvic floor was reached.

Similarly, rotation of an occiput posterior into the hollow of the sacrum and spontaneous delivery thereof, be the patient primipara or multipara, does not materially delay the completion of the delivery.

In the remaining groups, that is, those in whom internal rotation is only partly accomplished, or in whom no rotation takes place (2.6 per cent of primiparas and 1.4 per cent of multiparas), failure of rotation is a much more significant item in primiparas but not of serious import in multiparas. Even in primiparas, it is not of great importance if the labor pains are good, but if the labor pains are poor, forceps delivery was thought necessary in 75 per cent of our primiparas.

TABLE II. SECOND STAGE IN MULTIPARAS

PELVIC FLOOR PHASE		TIME (MINUTES)	NUMBER OF PATIENTS
<i>Good pains:</i>			
Small baby	Early rotation	8.7	716
Small baby	Early rotation	add 3.0	272
Large baby	Early rotation	9.5	434
Large baby	Early rotation	add 3.5	174
<i>Poor pains:</i>			
Small baby	Late rotation	12.1	349
Small baby	Late rotation	add 8.1	186
Large baby	Late rotation	14.7	235
Large baby	Late rotation	add 6.6	125

\*Labor pains were said to be good for the purposes of this study if they occurred at intervals no longer than two minutes and of an intensity that would barely allow a slight indentation of the fundus of the uterus by the examiner's finger at the height of a contraction and at a point not directly over the body of the baby. They were said to be poor if of a longer interval or a lesser intensity, or both.

without any considerable delay and without harm to mother or baby. Thirty-two out of 42 similar multiparas delivered spontaneously with labor prolonged no more than a few minutes as a result of the unrotated position of the head. The remaining 75 primiparas and 10 multiparas were delivered by operative means. It could well be that a considerable portion of these latter groups would have rotated and delivered spontaneously had the application of forceps or manual rotation been delayed a few more minutes. (These latter four groups of patients—that is, those rotating anteriorly [either soon or a little later] after reaching the pelvic floor, those rotating posteriorly, those undergoing partial rotation, and those undergoing no rotation will hereafter be referred to collectively as “Late Rotation.”)

### When (and Why?)

As stated above, internal rotation occurs in approximately two-thirds of all patients by the time the head has reached the pelvic floor. In the remaining one-third, it occurs later or, perhaps, not at all. Whereas internal rotation has taken place during the first stage of labor in a very small percentage of all patients, it is, for the most part, very definitely a second-stage phenomenon. In this connection, several statements in a previous publication<sup>1</sup> will not be repeated here. The long-standing belief that only small round heads sometimes failed to undergo internal rotation is not borne out by this study. Not only does the same proportion of large heads (weight 3,500 Gm. and over) rotate, but the rotation occurs at approximately the same time, so that the size of infant's head or size of the infant is not a factor in this process. Similarly, failure of rotation occurs with occiput anterior as well as with occiput posterior. It is only slightly more frequent with the posterior position. Somewhat to our surprise (Table I), we found that early rotation was definitely more frequent in multiparas than in primiparas. What was even more interesting was the

TABLE I. INTERNAL ROTATION

		INCIDENCE OF LATE ROTATION (PER CENT)	
<i>Primiparas:</i>			
Good pains	Small babies	772 Early	
		374 Late	33
	Large babies	229 Early	
		121 Late	35
Poor pains	Small babies	592 Early	
		432 Late	42
	Large babies	234 Early	
		163 Late	41
<i>Multiparas:</i>			
Good pains	Small babies	716 Early	
		272 Late	28
	Large babies	434 Early	
		174 Late	29
Poor pains	Small babies	349 Early	
		186 Late	35
	Large babies	235 Early	
		125 Late	35

tabulation, it would seem that operative delivery is rarely if ever necessary in multiparas, except perhaps in the group of large baby, late rotation, and poor pains, where approximately one out of sixteen such patients was so delivered in this series. In primiparas, we are more and more learning that forceps are not necessary where the labor pains are good, but are, perhaps, increasing our incidence of forceps deliveries in the presence of poor pains, particularly when the baby is large or rotation is late. In the complete absence of rotation, our forceps incidence was 75 per cent of that very small group of primiparas (2.6 per cent) where the pains were poor and the baby large (1.95 per cent of all primiparas). Even in this very small group, one should not proceed to the immediate application of forceps as soon as the head reaches the pelvic floor, or even in three to five pains thereafter, as a delay of thirty to sixty minutes will produce sufficient distention of the perineal tissues that the forceps delivery will be found to be much easier than if attempted immediately. Moreover, one is frequently surprised to find that rotation does occur at the end of thirty to forty minutes, when in the first fifteen or twenty minutes it had seemed most unlikely. The old rule of "not over one hour on the pelvic floor," as stated by Litzenberg, Baer, Polak, and others, is still a reliable rule.

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1. Calkins, L. A.: AM. J. OBST. & GYNEC. 48: 798, 1944.

### Discussion

DR. M. PIERCE RUCKER, Richmond, Va.—From a practical standpoint, I believe the shorter the second stage the better it is for mother and baby. If proper facilities and help are available, I see no reason why the mother should not be delivered as soon as the cervix is out of the way.

As a study in the physiology of labor, Dr. Calkins' essay is important, for when all is said and done, we cannot know too much of physiology. It is the standard by which we should measure our results. When the speaker states that in two-thirds of all patients internal rotation is complete at the time the head reaches the pelvic floor, and that in something less than 30 per cent, it is completed very shortly thereafter, we may take it that this represents the true state of affairs. In slightly over 4 per cent anterior rotation does not take place. Some of these rotate posteriorly, and in some anterior rotation is arrested, but in 3.4 per cent of all primiparas, and 1.7 per cent of all multiparas, no internal rotation occurs.

The statistical value of the paper is somewhat vitiated by the forceps deliveries. These varied from 1 per cent to 75 per cent in the various subgroups. Furthermore, the author does not state his indications for the operation. He is conscious of this possible criticism when he says that the "fact that we used forceps on 40 per cent of these patients (large babies with late rotation) explains the contradiction noted in Table III where late rotation seemingly prolongs the second stage by only ten minutes." Evidently his obstetric judgment got the better of his statistical zeal.

It is interesting to note that the size of the fetal head is unimportant from the standpoint of internal rotation or failure of rotation. The character of uterine contractions is of far greater importance. By inference the tenseness of the pelvic floor is not as important a cause of anterior rotation as we were taught to believe, for in multiparas failure of internal rotation occurs in only 1.2 per cent when the pains were good in comparison with an incidence of 2.6 per cent in primiparas. Furthermore, in two-thirds of all patients, internal rotation takes place before the presenting part hits the "pelvic trough" which we used to think was the cause of internal rotation.



Table II shows these differences for multiparas in simple tabular form. The group of large baby, late rotation, and poor pains should probably be looked upon as adding something like ten or twelve minutes to the duration of the early rotation group, rather than the 6.6 minutes recorded in the table.

Table III presents the same material for primiparas. It will be observed that significant prolongation of the pelvic floor phase of the second stage is present where the labor pains are poor. It should be noted that this difference of seventeen minutes observed in late rotation for small babies is, perhaps, not far from being entirely correct. Although approximately 25 per cent of the late rotations were delivered with forceps, only a very few could be said to have prolonged second stage in this operative group. Large babies with late rotation and poor pains present a considerably different picture. In this group, the labor may be considerably prolonged. The fact that we used forceps on 40 per cent of these patients explains the apparent contradiction noted in Table III, where late rotation seemingly prolongs the second stage by only ten minutes. This figure would undoubtedly be at least thirty to forty minutes if it were not decreased by frequent operative intervention.

TABLE III. SECOND STAGE IN PRIMIPARAS

PELVIC FLOOR PHASE			TIME (MINUTES)	NUMBER OF PATIENTS
<i>Good pains:</i>				
	Small baby	Early rotation	28.7	772
	Small baby	Early rotation	add 3.7	374
	Large baby	Early rotation	33.6	229
	Large baby	Early rotation	add 10.8	121
<i>Poor pains:</i>				
	Small baby	Late rotation	44.9	592
	Small baby	Late rotation	add 17.0	432
	Large baby	Late rotation	61.6	234
	Large baby	Late rotation	add 9.9	163

Careful appraisal of Tables II and III would suggest that poor pains is a much more significant item than failure of rotation, which is apparently of equal importance to "large" baby as a deterrent to prompt completion of the second stage. Although no data are here included, we also know from recent careful observation that voluntary effort is at least equally important to the labor pains.

Table IV presents the data for these same groups of patients with incidence of operative delivery, all but very few of which were low forceps. From this

TABLE IV. FORCEPS DELIVERIES IN PER CENT

			PRIMIPARAS	MULTIPARAS
<i>Good pains:</i>				
	Small baby	Early rotation	4.0	0.7
	Small baby	Late rotation	5.1	
	Large baby	Early rotation	4.4	
	Large baby	Late rotation	9.1	
<i>Poor pains:</i>				
	Small baby	Early rotation	15.5	2.2 2.5 6.4
	Small baby	Late rotation	24.3	
	Large baby	Early rotation	26.1	
	Large baby	Late rotation	39.9	

## THE OBSTETRIC MANAGEMENT OF PREGNANCY COMPLICATED BY HEART DISEASE\*

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THIS paper is a review of 200 cases of pregnancy complicated by heart disease. The majority of these patients has been observed in a cardiac and obstetric clinic which was established at the Toronto General Hospital in 1933. Some patients did not receive the benefit of such observation and care, and were first seen when admitted to the hospital because of cardiac failure or the onset of labor. One hundred ninety patients had rheumatic heart disease, seven had congenital heart disease, and three had degenerative heart disease.

The cases have been divided into three groups according to the severity of their heart disease. Group I is composed of patients without impairment or very slight impairment of exercise tolerance. Group II is composed of patients with moderate to severe impairment of exercise tolerance. Group III is composed of patients with extreme impairment of exercise tolerance or cardiac failure. The number in each group is shown in Table I.

TABLE I

Group I	87 cases
Group II	80 cases
Group III	33 cases

Patients attending the cardiac-obstetric clinic are requested to report for examination every two weeks, and are seen by the cardiologist every four weeks. All patients are advised to rest a minimum of twelve hours daily, and this is increased as the pregnancy progresses or the exercise tolerance diminishes. If adequate rest cannot be obtained at home, the patient is sent into the hospital. Most patients in Group II are advised to come into the hospital for rest about one week before their expected date of confinement. Patients are warned of the seriousness of upper respiratory infection and advised to take more than usual care if such infection occurs. When possible, the normal gain in weight during pregnancy is limited by suitable diet to fifteen pounds. If the patient is obese, an effort is made to prevent any gain in weight. The development of signs of the late toxemias of pregnancy is considered serious, and immediate admission to the hospital is recommended for even mild degrees of albuminuria and hypertension. By such a regime, 170 patients have been carried to the period of viability or full term.

Thirty patients, all in Group II or III, had their pregnancies terminated before the sixth month. The indications for termination are shown in Table II.

\*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

I wish Dr. Calkins had discussed the role of the uterus, other than its driving power, in the failure of internal rotation. He stated internal rotation was usually a second stage phenomenon. Can it be that so long as the presenting part is within the uterus, the lower uterine segment acts as a brake on rotation?

The more we study the physiology of labor, the more we feel the need of further study of the uterus. In the past, attention to mechanical difficulties has overshadowed the importance of variations in the function of this organ. Today's paper is a case in point. The character of the labor pains is of greater importance than the size of the fetal head or the character of the perineum.

DR. CALKINS (Closing).—This paper deals with patients whose pelves (in over 90 per cent) were normal. We did not delete any abnormal pelves from the series, and it can well be that a truly abnormal pelvis will definitely affect the physiology of labor. Certainly, anything that is out of the usual may be a factor, since we as yet do not know the etiology of internal rotation itself. I cannot, therefore, answer the question as to what effect the various types of pelvis may have upon the mechanism of labor. I am trying to find out what happens when the pelvis is normal, and I still do not know. This study is only a step in that direction.

As to the question whether one may by simple finger pressure on the suture line bring about more prompt rotation, there is no question but that such can be done, particularly when rotation will otherwise be early and easy, but it cannot be so readily effected with the large head and poor pains, and that is when you really need some help.

would probably be allowed to proceed to term. Our more recent experience is similar to that of Hamilton and Thomson,<sup>1</sup> who found that during the last month of pregnancy there is a lessening of the cardiac strain, which is usually accompanied by clinical improvement in the condition of the patient.

Our present policy in the management of the cardiac patient during labor is to give sufficient sedative during the first stage to relieve pain and anxiety and provide adequate rest. The exhausting second stage is frequently shortened by forceps delivery under ether and oxygen or cyclopropane anesthesia. It is recognized that there is an increased danger of postpartum collapse and hemorrhage, and particular care is exercised to avoid this complication of the final stage of labor. Prior to 1933, we were of the opinion that cesarean section with sterilization was the method of choice for the delivery of the cardiac patient. Between 1928 and 1933 cesarean section was employed in 19 of 41 cases of heart disease, an incidence of 46 per cent. The method of delivery of these patients is shown in Table IV.

TABLE IV. METHOD OF DELIVERY 1928 TO 1933—41 CASES

Cesarean section	19
Forceps	6
Spontaneous	16

After a review of these cases published in 1933,<sup>2</sup> it was concluded that this high incidence of cesarean section was unjustified. Since that date cesarean section has not been performed because of heart disease. One hundred twenty-eight patients suffering from heart disease have been delivered, and cesarean section was employed only on three occasions, once for placenta previa, once for toxemia, and once because of previous cesarean section. The method of delivery of these 128 cases is summarized in Table V.

TABLE V. METHOD OF DELIVERY—128 CASES

Spontaneous	68
Forceps	57
Cesarean section	3

Most patients tolerated labor surprisingly well, and in no case did labor alone appear to precipitate cardiac failure. In Group II there were five patients whose labor lasted over thirty hours and in one of these, with a twin pregnancy, the duration of labor was fifty hours. Despite this, however, recovery was satisfactory in all five. In eleven cases postpartum hemorrhage developed. In five of these the hemorrhage was extremely severe and one of these patients died.

During the puerperium, all patients are advised to remain in bed for fourteen days. Patients in Groups II and III are given more prolonged bed rest according to their individual requirements.

There were eight deaths in the 200 cases, a mortality rate of 4 per cent. Four of the deaths occurred in patients who had not attended the prenatal clinic, had received inadequate or no care during pregnancy, and were first

TABLE II

Failure before present pregnancy	5 cases
Failure during present pregnancy	7 cases
Marked and progressive impairment of exercise tolerance	17 cases
Acute rheumatic fever and severe myocarditis	1 case
Total	30 cases

Definite indications for the termination of pregnancy have not been established, but each case is individually assessed by considering the past cardiac and obstetric history, parity, and the present cardiac status of the patient. Twelve patients who had had cardiac failure before becoming pregnant or who developed it during the early months had pregnancies terminated after recovery from the failure or when marked improvement in their general condition had occurred. Seventeen patients had pregnancies terminated because of such marked impairment of exercise tolerance that it appeared that the added burden of late pregnancy would be greater than the heart could stand. One patient with severe myocarditis had pregnancy terminated during an acute attack of rheumatic fever. Of the 30 patients in whom pregnancy was terminated, only two were primiparous, and 20 were para two or more.

Further pregnancies are inadvisable for the majority of patients requiring therapeutic abortion because of heart disease. It is therefore advantageous to combine sterilization and therapeutic abortion if the former can be done without increased risk. This was accomplished in 22 of the 30 cases, either by hysterectomy, fundectomy, or hysterotomy with varying types of tubal resection.

TABLE III. METHOD OF TERMINATION

Dilatation and curettage	5 cases
Hysterotomy and tubal ligation	3 cases
Fundectomy	4 cases
Hysterectomy	15 cases
Bag induction	3 cases
Total	30 cases

All these cases made a satisfactory postoperative convalescence except one who, although she ultimately recovered, developed a pulmonary embolus. In eight cases the general condition of the patient was so poor that sterilization was not undertaken. In five of these the pregnancy was of three months or less duration, and termination was accomplished by dilatation and curettage. In the remaining three patients, however, the pregnancies were between four and six months, and labor was induced by rupture of the membranes and the insertion of a bag. One of these patients died from cardiac failure thirty days after termination.

Of the 170 patients who reached the period of viability, 87 were in Group I, 62 in Group II, and 21 in Group III. There was one case of twin pregnancy, one case of placenta previa, and four cases of severe pre-eclamptic toxemia. Forty patients went into premature labor. Of these, two were induced because of pre-eclamptic toxemia, and two were induced because of heart disease. These last two patients were both about seven and one-half months pregnant and appeared early in the series. At the present time they

final outcome of any case in this series. On the contrary, the avoidance of a serious abdominal operation, carrying with it an appreciable operative mortality in a "poor risk" patient, has probably contributed to a lessening of both morbidity and mortality.

The large number of cases (40) of premature labor which resulted in a fetal mortality of 17 per cent is worthy of note. Such a high fetal loss among a group of patients in whom repeated pregnancies are inadvisable is disturbing. The only apparent solution is more rest in bed during the seventh and eighth month for all patients in Group II.

The large number of pregnancies terminated (30 cases) warrants comment. Because of serious heart disease, many patients were referred for therapeutic abortion to the cardiac-obstetric clinic by their own physicians, and this undoubtedly has increased the incidence of terminated pregnancies. Patients who have had cardiac failure or who develop it during the early months of pregnancy are very unlikely to stand the added burden of late pregnancy without another cardiac breakdown. Twelve of the cases were in this category, and therapeutic abortion seemed clearly indicated. Seventeen patients had such marked impairment of exercise tolerance early in pregnancy with other clinical evidence of serious heart disease that termination was deemed advisable. There are many aspects to the problem of therapeutic abortion other than medical, and each individual problem was carefully considered and discussed with the patient herself. Every effort was made to carry to term the primiparous patient, even in the face of apparently grave risk; whereas, with the multiparous patient—the mother of two or more children—such a risk was considered unjustified. Twenty of the thirty patients in whom pregnancy was terminated had two or more living children, and only two were primiparas.

The occurrence of late toxemia in the pregnant patient with heart disease is an added serious complication and may be the initiating factor in the development of cardiac failure. It frequently occurs just at the time when the strain of pregnancy on the heart is greatest and when induction of premature labor is least desirable. Prompt hospital treatment, for even the mildest cases, and wise selection of patients for induction of labor will minimize the danger and risk to the mother.

### Summary

Two hundred cases of pregnancy complicated by heart disease have been analyzed. The mortality rate for the whole group was 4 per cent, while for those patients under our control throughout pregnancy the rate was 2.2 per cent. Thirty patients had pregnancy terminated because of heart disease, and 170 patients reached the period of viability. In 40 of these the onset of labor was premature, and this resulted in a fetal mortality of 17 per cent. During recent years heart disease has not been considered an indication for cesarean section. One hundred twenty-eight consecutive cases of heart disease have been delivered and cesarean section employed on only three occasions, all for

seen by us on admission to the hospital. Two were multiparas in advanced labor with cardiac failure, one was delivered spontaneously, and the other by low forceps. Both died within twelve hours of admission to hospital. One patient, eight months pregnant, died undelivered twelve hours after admission, and the postmortem examination revealed rheumatic heart disease, bacterial endocarditis, and cardiac failure. The fourth patient was admitted in coma due to late toxemia of pregnancy. After twenty-four hours in the hospital without improvement, delivery was accomplished by cesarean section. This was recognized at the time as a desperate venture, and the patient died seventy-two hours later with pulmonary edema without regaining consciousness.

The remaining four patients who died were under our control throughout pregnancy. The first had no symptoms of heart disease and died as a result of postpartum hemorrhage. The second developed cardiac failure during the eighth month, improved slightly at term, and stood a relatively short labor and low forceps delivery very well. There was a slight improvement in the patient's condition at the end of the first week post partum, followed by a gradual relapse and death on the twenty-seventh day. The third patient went into premature labor at the eighth month during cardiac failure and had a short six-hour labor and spontaneous delivery. This patient died on the sixtieth day post partum from auricular fibrillation, multiple emboli, and cardiac failure. The fourth patient died from cardiac failure one month after termination of a four and one-half month pregnancy by bag induction.

### Discussion

A mortality rate of 4 per cent for 200 cases of pregnancy complicated by heart disease emphasizes the gravity of this complication. If those patients who were not under our care for the prenatal period are excluded (21 cases), the mortality is reduced to 2.2 per cent, which corresponds closely to the mortality reported by Hamilton and Thomson,<sup>3</sup> who state that a 2 per cent mortality probably represents the minimum rate that can be expected in a large group of patients, even when well managed. Excluding the one patient (aged 21 years) who died from hemorrhage and was in Group I, all patients who died were more than 32 years of age, and the average age was 38.8 years. The average age of all patients reaching the period of viability was 26 years. It would appear that it is the older patient who faces the greatest risk during pregnancy. The average age of death (38.8 years) for the eight patients in this series is one year more than the average age of death of 56 consecutive female deaths due to rheumatic heart disease not associated with pregnancy taken from postmortem records of the Toronto General Hospital. This suggests that while pregnancy may be the initiating cause of cardiac failure and death in a patient with heart disease, it does not reduce the average age of death for a group of patients suffering from heart disease. Proper management during the prenatal period and the wise selection of cases for the termination of pregnancy during the early months would appear to be the prime factors in establishing a low mortality rate. The choice of vaginal delivery rather than cesarean section has not apparently unfavorably influenced the

## THE PROBLEM OF TALCUM GLOVE POWDER AND CONTRA-INDICATIONS FOR ITS EMPLOYMENT\*

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**I**N SURGERY, as in every other field of endeavor, there is a constant need for resisting the temptation to take anything for granted. True progress demands the discovery and correction of old errors as well as the pursuit of new ideas. New light brought to bear upon an old situation may produce a new fact. Advantage should be taken of every opportunity to re-examine all links in the chain between cause and effect, the old as well as the new. When this is done, the backward glance will often prove to be as rewarding as the forward glance.

These observations are suggested by the results of an extension of the inquiry into the use of magnesium silicate (talcum) as a powder for gloves and other rubber articles extensively used in modern operative procedures.

Until quite recently, magnesium silicate was a substance whose role was never questioned. It played a small but seemingly benign part in the assembly of hands and materials that function in operative procedures.

The studies reviewed in this paper confirm the earlier conclusion that magnesium silicate in its application as a dusting compound for rubber gloves is a mischief-maker that should be eliminated and replaced with a safe and reliable substitute.

It has been previously demonstrated by Lambert<sup>1</sup> and by others<sup>2</sup> that magnesium silicate in the form of dusting powder acts as a foreign body irritant when it gains entrance into the body tissues. The number and the size of the crystals determine the extent of the reaction. One or more fine particles of the silicate will form lesions seen under the microscope as small fibrotic areas. When the powder has been introduced in larger quantities, large and definitely granulomatous lesions with typical foreign body giant cells will be observed.

The trouble-making crystals themselves may then be seen in these lesions between rather dense fibroblastic connective tissue bundles or in the giant cells that are produced as Nature attempts to wall off the offending substance and remove it from the body.

Unfortunately, the attempt at a purge falls short of success. The nature of magnesium silicate is such that the substance may be expected to remain within the tissues once it has found a lodging place, and it will continue to act as an irritant until it is removed.

Our previous reports have described the action of magnesium silicate in producing peritoneal adhesions after abdominal surgery, and also upon its effects

\*Presented at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.



obstetric indications. The average age of death in the whole series was 38.8 years. The average age of death of 56 consecutive female patients, proved at autopsy to have died from rheumatic heart disease not associated with pregnancy, was one year less.

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inflammatory reaction generated by magnesium silicate crystals deposited by the gloved hands or drains at the time of operation.

Only a partial list of the cases studied in this series is submitted with this report, but we deem it sufficiently conclusive to merit the observation that no reason remains for not giving the situation the attention it deserves.



Fig. 3.—Granulomatous and fibrotic area around small subcutaneous vessels. Crystals difficult to see without polarized lighting.

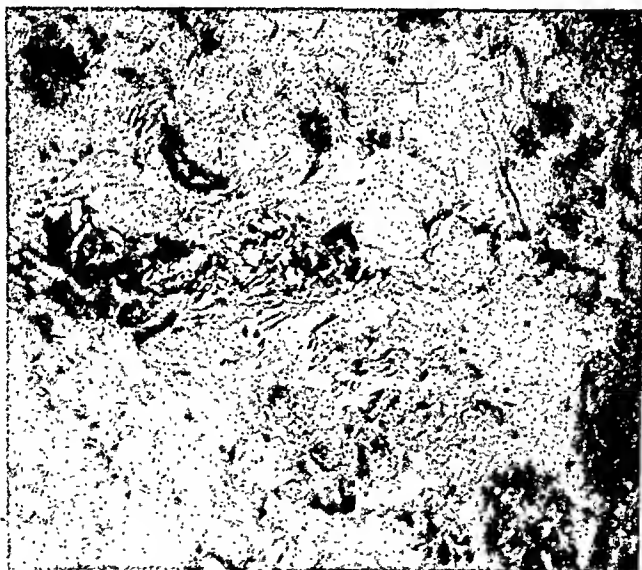


Fig. 4.—Same area as Fig. 3, as seen using polarization of light. Crystals of magnesium silicate plainly visible.

Our viewpoint simply is this — whenever the abdomen has been opened and the omentum or other tissue has been handled by the previously powdered gloved hand of the operating surgeon, careful study will demonstrate the presence of magnesium silicate crystals and a resulting reaction as described.

in other areas, for instance, the nonhealing sinus tracts left along surgical incisions into the deeper tissues.

The finding of magnesium silicate crystals in scars removed by surgery inspired a subsequent study of all old healed incisional scars removed surgically after a period of several months in various hospitals. We have not been surprised to discover that in every scar so removed, definite lesions containing magnesium silicate crystals could be demonstrated.

As a result of these findings we feel free to conclude that many of our cases exhibiting postoperative incisional pain and tenderness may be charged to



Fig. 1.—Small fibrotic area around small nerves in subcutaneous tissue beneath old scar.



Fig. 2.—Foreign body giant cell and granulomatous reaction; subcutaneous area beneath resected recent operative scar.

We have presented a study of resected postoperative incisional scars and omental fat showing chronic granulomatous lesions with foreign body reaction and crystals of magnesium silicate in practically every case.

We urge the adoption of a technique to minimize the hazards of magnesium silicate in surgery.

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Beyond that point, there is no need to elaborate upon the previously reported papers covering magnesium silicate reactions. Quite plainly, it should be well recognized by this time that magnesium silicate is a harmful substance and should have no further place in the surgical procedure of our hospitals.

We may look with confidence to chemistry for an alternative substance that will serve the necessary function of a dusting compound without intruding the nonabsorbable and irritating crystalline properties of magnesium silicate. It is desirable that the substitute should be soluble in the body fluids and, at the same time, impervious to change in the sterilizing process.

Until the introduction of a substitute, practical considerations require a technique for avoiding damage for magnesium silicate. We believe that this end can be achieved by a very sparing use of cream of tartar on the hands before they are inserted into the gloves and by thorough washing of the hands after they have been gloved.

The technique we have devised for use in St. Vincent's Hospital is as follows:

1. Only enough magnesium silicate powder is applied to the inside of the gloves before dry sterilization to avoid the adhesion of their surfaces during the sterilizing process.

2. Cream of tartar is applied to the hands in small quantities, enough to assist the hands into the sterile gloves.

3. All powder remaining on the external surface of the gloves is removed by washing through two basins of sterile water.

4. All other rubber articles required in the operation are sterilized by boiling, and no powder applied.

This procedure appears to remove all but the smallest particles of the magnesium silicate powder. We submit that its observance pending the development of a substitute powder will produce a proportionate reduction in the number of postoperative lesions.

We submit several microphotograph findings in excised old and recent scars studied since 1943 at our institution, taken from the last one hundred cases.

The use of Polaroid in two planes of the microscopic light source in the manner suggested for our polarizing microscopes will aid materially in finding magnesium silicate crystals in the tissues.

Accessory parts for this purpose, cap polarizers and disc polarizers, are available and can be used with any of our modern microscopes. Properly rotated, they polarize the light in such a manner that any refractile substance in the path of the rays will be brought into clear vision. Without polarized light, many small crystals will remain invisible. Large crystals in giant cells may be observed with ordinary illumination, but in many cases cannot be studied in satisfactory detail without polarized light.

### Summary

We have again called attention to the harmful effects of magnesium silicate when introduced into the body tissues in the form of surgical glove powder.

TABLE I. SYMPTOMS AND SIGN

	SYMPTOMS					CARDIOVASCULAR CHANGES			
	ONSET IN GESTATION	HEAD-ACHE	SCOTOMAS AND DIPLOPIA	EPIGASTRIC PAIN	EDEMA	BLOOD PRESSURE		HEART	PERIPHERAL VESSELS
						SYSTOLIC	DIASTOLIC		
<i>Mild</i> Hypertensive Disease, Hypertensive Cardiovascular Disease <i>Severe</i>	before 24 weeks	slight or absent	absent	absent	slight or absent	under: 160 (often improves with rest)	100	normal or slightly larger	normal or slight change
	before 24 weeks	present, often severe	usually present	absent	usually present	over: 160 (persistent after rest)	100	enlarged	hypertensive retinitis
<i>Mild</i> Pre-eclampsia	after 24 weeks	slight or absent	absent	absent	slight or absent	140-160 (often not persistent)	90-100	normal	normal
<i>Severe</i> Pre-eclampsia	after 24 weeks (may be earlier with mole)	present usually severe	present usually severe	often present (late)	moderate to severe	over: 160 (usually persistent)	100	may be enlarged	hypertensive retinitis may be present
Nephrosclerosis; Chronic Vascular Disease	before 24 weeks	present mild	present mild	absent	absent	over: 140 (persistent, may be mild)	90	normal	albuminuric retinitis
<i>Acute</i> Glomerulonephritis	often history of acute onset	absent	absent	absent	slight or absent	elevated	elevated	normal	normal
	(all findings may be transient and present only in the acute phase)								
<i>Chronic</i> Glomerulonephritis	prior to gestation	absent	absent	absent	slight	elevated	elevated	normal	retinitis
Nephrosis	prior to gestation	absent	absent	absent	present, marked	slight, if any increase		normal	retinitis may occur

## Group B: Diseases dependent on or peculiar to pregnancy

## I Pre-eclampsia

- (a) mild
- (b) severe

## II Eclampsia

- (a) convulsive
- (b) nonconvulsive (i.e., coma with necropsy findings typical for eclampsia)

## Group C: Vomiting of pregnancy

## Group D: Unclassified toxemia

The symptoms and signs commonly associated with the diseases listed in the classification have been tabulated (Table I) for comparison and study.

The diseases not peculiar to pregnancy are considered pseudotoxemias and are included in the classification because "the underlying pathologic lesion or lesions of each of these diseases tend to be aggravated by the increased physiologic demands of the pregnant state and tend to produce symptoms one or more of which simulate those of preeclamptic toxemia and/or of eclampsia, or of both." Differentiation of the "true" from the "false" toxemias is often difficult, and requires careful study and evaluation.

## Original Communications

### A DISCUSSION OF CLASSIFICATION OF TOXEMIAS OF PREGNANCY

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(From the Margaret Hague Maternity Hospital)

THE importance of proper diagnosis and classification of disease processes is acknowledged. Often the deterrent to any advances in therapy and prognosis of a particular disease is lack of understanding of the basic pathology involved. In the human being, the underlying pathology is reflected in subjective and objective symptomatology. Any classification based, all or in part, on subjective symptoms must of necessity be fallacious, inasmuch as the personal factor in expressing subjective symptoms, both as to presence and degree, is not reliable enough to be scientifically accurate.

In order to accomplish a proper evaluation of the various toxemias of pregnancy for the purpose of setting up an adequate therapeutic regime and offering accurate prognosis, it is very important to base the classification of the particular toxemia on unequivocal objective evidence.

There have been many classifications of the so-called "toxemias of pregnancy." The various authors have found that, despite their efforts to make their classifications complete and thorough, some shortcomings could usually be demonstrated. This discussion is for the purpose of illustrating how we may better use an existing classification. An attempt will be made to show that on the basis of objective information the various toxemias can be fairly accurately differentiated. A suggestion for modification of the present classification of toxemias will be offered.

The "Classification of the Toxemias of Pregnancy" as outlined by the American Committee on Maternal Welfare and published in 1940<sup>1</sup> has been used as the basis for this discussion. The classification as set up by this committee is as follows:

Group A: Diseases not peculiar to pregnancy

I Hypertensive Disease (hypertensive cardiovascular disease)

- (a) benign (essential)
- (b) malignant

II Renal Disease

- (a) chronic vascular nephritis (nephrosclerosis)
- (b) glomerulonephritis
- (c) nephrosis
- (d) other forms of severe renal disease

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

tic. However, hypertension may persist following pre-eclampsia, confusing differentiation, often for many months.<sup>2</sup>

Comparison of severe hypertensive disease with severe pre-eclampsia will elicit a like set of facts and differentiation is sometimes difficult, especially if the first sign of disturbance occurs after 24 weeks gestation. The more pronounced edema, proteinuria, and frequent oliguria in severe pre-eclampsia often serve to differentiate the two. The hypertensive with considerable proteinuria, not cardiac in origin, is usually in some degree of renal failure and has a diminished urea clearance. The urea clearance usually remains normal in the pre-eclamptic.<sup>3</sup> Absolute differentiation can be made only if: (1) hypertension occurs early in the first trimester (in hypertensive disease); or (2) the whole pattern disappears early in the puerperium (pre-eclampsia) (Table II).

Nephrosclerosis or chronic vascular disease occurs in the first 24 weeks of pregnancy and, more often, long before that time. Although some of the findings are common with those found in hypertensive disease (before the nephrosclerotic phase) or in pre-eclampsia, there are several items that are characteristic enough to be differential (Table III). Albuminuric retinitis is severe in nephrosclerosis and more marked than seen in the other conditions, although hypertensive retinitis may occur in the severe hypertensive or pre-eclamptic. In nephrosclerosis, urinary specific gravity is always below 1.020, and often remains low and fixed and the urea clearance is low. In severe hypertensive disease, the specific gravity of the urine as well as the urea clearance is lowered. Of course, one must be mindful that in the late stages of severe hypertensive disease we actually are dealing with a "chronic vascular disease" so that differentiation from nephrosclerosis may be impossible. In severe pre-eclampsia, urinary specific gravity and urea clearance are normal. Persistence after puerperium differentiates nephrosclerosis from pre-eclampsia.

TABLE III. DIFFERENTIATION OF NEPHROSCLEROSIS, HYPERTENSIVE DISEASE, AND PRE-ECLAMPSIA

	NEPHROSCLEROSIS	HYPERTENSIVE DISEASE	PRE-ECLAMPSIA
Occurrence	Before 24 weeks gestation, usually	Any time, before 24 weeks gestation usually	After 24 weeks gestation
Persistence	After pregnancy	After pregnancy	Disappears after pregnancy
Retinitis	Albuminuric, marked	Hypertensive, may occur if severe	Hypertensive, may occur if severe
Urine specific gravity	Always less than 1.020, often fixed	May be lowered, if severe	Normal
Urea clearance	Low	May be lowered	Normal

Glomerulonephritis with its history of acute onset, often febrile, is characteristically differentiated from the other renal diseases by the transient hypertension and the urinary findings of red blood cells and casts. The acute phase is rare in pregnancy. The chronic phase resembles mild pre-eclampsia, but urinary casts and red blood cells along with diminished renal function are differential.

Nephrosis is characterized by a marked edema with little, if any, elevation in blood pressure. Study of the blood serum reveals low protein and high



OF TOXEMIAS OF PREGNANCY

RENAL FUNCTION	ALBUMIN- URIA	SPECIFIC GRAVITY URINE	MICRO- SCOPIC URINE	BLOOD CHEMISTRY				RESPONSE TO TREATMENT
				URIC ACID	NON- PROTEIN NITROGEN	RATIO URIC ACID /N.P.N.	CO <sub>2</sub> COM- BINING POWER	
normal	trace only	normal	negative	normal	-----	(may be up)	-----	Good
often im- paired	trace usu- ally	may be lowered	negative	normal	-----	(may be up)	-----	Fair to poor
normal	under 6 Gm./L. (2+)	normal	negative	may be high	normal	often up	normal	Usually good
normal or slightly impaired	over 6 Gm./L. (3, 4+)	normal	casts and red cells may occur	usually high	normal	usually up	often de- creased	Blood pressure often increases despite diminishing edema
impaired	present	under 1.020 (urea clearance low)	usually negative	increased if severe	-----	may be up	may be low	Poor
may be im- paired	present	normal high or low	casts and red cells	may be normal or increased				Usually good
progres- sive failure	present	usually low	casts and red cells	increased	-----	normal	often low	Fair to poor
often nor- mal	marked	often high	no casts or cells	normal (in serum: low protein high cholesterol)	-----	-----	-----	Poor

Comparing mild hypertensive disease with mild pre-eclampsia (Tables I and II) one notes that all the findings are fairly common, except the time of onset of the symptoms. Hypertensive disease may manifest itself before twenty-four weeks gestation, pre-eclampsia usually after twenty-four weeks. However, in any of the diseases "not peculiar to pregnancy" the appearance of symptomatology may be after twenty-four weeks, not because the disease is due to the pregnancy, but because the pregnancy may have served to light up already existing pathology. Therefore, the differentiation of these two is difficult and often impossible during the pregnancy. Following the termination of the pregnancy, the persistence of any or all the signs for more than 12 to 16 weeks, or a similar designated arbitrary period, will make it probable that the disease is not peculiar to pregnancy, and therefore hypertensive rather than pre-eclamp-

TABLE II. DIFFERENTIATION OF HYPERTENSIVE DISEASE FROM PRE-ECLAMPSIA

HYPERTENSIVE DISEASE	PRE-ECLAMPSIA
1. Onset before 24 weeks gestation	1. Onset after 24 weeks gestation
2. Persistence after pregnancy	2. Disappearance after pregnancy

than 6 Gm. per liter, or more than mild edema. Thus, the occurrence of one incident of findings in the "severe" category is not valid evidence for classifying a pre-eclampsia as severe.

It must be emphasized at this time that the differentiation between "mild" and "severe" pre-eclampsia is of hardly more than academic interest. Actually the differentiation should be dropped from the classification entirely. Cosgrove and Chesley, in discussing the relationship of eclampsia to the diagnosis of the toxemia prior to convulsion, state that "one cannot assume that a case of mild pre-eclampsia is in no danger of eclampsia . . . almost two-thirds of all our eclampsia occurred in cases which we had considered mild pre-eclampsia . . . one out of every 29 of our mild pre-eclampsics became abruptly eclamptic without any intermediate phase which would warrant their consideration as severe pre-eclampsics."<sup>4</sup>

It is worthy of note, and regrettable, that the classification fails to make use of the blood chemistry findings in pre-eclampsia as an objective yardstick for the prognostic evaluation of the toxemia.

Standar and Cadden conclude that "frequently repeated blood chemistry studies in 108 eclamptic and 40 pre-eclamptic patients . . . show that the blood chemistry is an indispensable index of the severity of the disease and of the specific treatment needed."<sup>5</sup> Our experience has shown that the clinically so-called "mild" pre-eclampsia may, by virtue of the deterioration of blood chemistry values, serve notice of the actual severity of the biochemical disturbance, and therefore warrant considerably more concern than the triad blood pressure, proteinuria, and edema might suggest.

Chesley has pointed out that a uric acid/nonprotein nitrogen ratio exceeding 10 per cent is indicative of renal impairment.<sup>6</sup> In reviewing a random five-year period (1935-1939) at the Margaret Hague Maternity Hospital, it was noted by the author that there were 90 cases of eclampsia, of which 35 were in the hospital before the first convulsion. Of these 35, 23 (65.6 per cent) were classified as "mild pre-eclampsia" before the first convulsion.

Thirteen eclampsics of this group, definitely classifiable as mild pre-eclampsics prior to convulsion, had blood chemistries taken before the first convulsion (Table V). All thirteen of these patients had a uric acid/nonprotein nitrogen

TABLE V. BLOOD CHEMISTRY VALUES IN ECLAMPTIC PATIENTS PRIOR TO CONVULSION

PATIENT	DAY OF BLOOD CHEMISTRY BEFORE CONVULSION	URIC ACID MG./%	NONPROTEIN NITROGEN MG./%	URIC ACID/N.P.N. RATIO (%)
1	3	4.4	30.3	14.6
2	Day of	5.6	38.0	14.8
3	Day of	6.0	45.0	13.4
4	Day of	6.4	48.0	13.4
5	4	4.4	34.0	13.0
6	Day of	6.8	29.4	23.1
7	6	5.4	33.0	19.4
8	Day of	5.6	34.0	16.5
9	13	4.6	36.0	12.8
10	Day of	5.0	34.0	14.7
11	8	5.0	27.0	18.5
12	Day of	6.7	32.0	21.0
13	1	6.0	48.0	12.5

cholesterol. The disease may occur early and persist entirely unrelated to the pregnancy.

The aggravation of existing hypertension, proteinuria, and edema in the diseases "not peculiar to pregnancy" occurring after twenty-four weeks gestation must be construed to indicate the presence of superimposed pre-eclampsia.<sup>2</sup> Thus, a "true toxemia" is grafted onto the existing "pseudotoxemia." The return of values to prepregnancy levels during the puerperium or shortly thereafter corroborates such a diagnosis. Thus, the patient with uncomplicated essential hypertension whose blood pressure rises significantly (more than 20 mm.) and who also develops proteinuria and edema can be considered to have pre-eclampsia superimposed upon the essential hypertension, especially if in, or after, the puerperium the edema and proteinuria disappear and leave only the hypertension, at prepregnancy level.

Apart from the differentiation of those diseases peculiar to pregnancy from those independent of it, the classification also differentiates mild from severe pre-eclampsia. One may often be misled by the subjective complaints of the patient into considering her condition "mild" pre-eclampsia when, objectively, severe pre-eclampsia exists. Catastrophically, eclampsia may occur in patients demonstrating no objective findings other than those of mild pre-eclampsia.

TABLE IV. DIFFERENTIATION OF MILD AND SEVERE PRE-ECLAMPSIA

PRE-ECLAMPSIA	EDEMA	BLOOD PRESSURE		PROTEINURIA	RESPONSE TO THERAPY
		SYSTOLIC	DIASTOLIC		
Mild	Slight or absent	140 to 160 (often not persistent)	90 to 100	Less than 6 Gm./ liter (2+)	Usually good
Severe	Moderate to severe	Over 160	Over 100 (usually persistent)	More than 6 Gm./ liter (3 to 4+)	Blood pressure often increases despite di- minishing edema

If only objective findings are adhered to, the criteria of mild and severe pre-eclampsia are clear cut and definite. (Table IV.) The mild pre-eclamptic patient has slight or absent edema, a blood pressure over 140/90 that may go to 160/100, but is often not persistently elevated, and a proteinuria up to 6 Gm. per liter, i.e., 2+. Put to bed under the proper regime, this patient usually improves all these findings. The severe pre-eclamptic patient has moderate to severe edema, a blood pressure over 160/100, and more proteinuria than 6 Gm. per liter, i.e., 3 to 4+. Put to bed and treated, the severe pre-eclamptic may improve somewhat, but not nearly to the degree that the mild pre-eclamptic does, and often the high blood pressure persists or increases despite diminishing edema or proteinuria.

The diagnosis of pre-eclampsia should be based on the occurrence of two of the three objective findings: hypertension of 140/90, edema, and proteinuria, preferably when the patient is not in labor, but may be made if elevation of blood pressure or proteinuria occurs on two separate observations twenty-four hours apart. It is felt justified to make a diagnosis of severe pre-eclampsia if on two separate observations, at least twenty-four hours apart, not during labor, two of the three criteria are valid, that is, blood pressure over 160/100, more proteinuria

5. The importance of proper diagnosis and classification of toxemias of pregnancy has been stressed; the value of accurate classification for therapy, prognosis, and statistical study has been emphasized.

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ratio exceeding 10 per cent (12.5 to 23.1 per cent). In a summary of the blood chemistry findings in the 108 eclamptic patients studied by Stander and Cadden, the average uric acid/nonprotein nitrogen ratio was 12.6 per cent before convulsion, and 16.9 per cent during convulsion. Moreover, in reviewing the blood chemistry findings in 20 consecutive eclamptics in the same series of 108 eclamptic patients, it was found that all 20 had uric acid/nonprotein nitrogen ratios exceeding 10 per cent (13.7-21.6 per cent) in blood chemistries taken during the convulsion.<sup>5</sup> These statistics point up the necessity of including blood chemistry values in the criteria for the classification of toxemias of pregnancy.

Therefore, the diagnostic criteria of toxemia of pregnancy should be: (1) blood pressure, (2) proteinuria, (3) edema, (4) blood chemistry. If the diagnosis of pre-eclampsia is valid, by the present standards, it should be classified and considered severe if the uric acid/nonprotein nitrogen ratio exceeds 10 per cent.

Eclampsia of the convulsive type is self-explanatory. The findings of pre-eclampsia to which is added a convulsive seizure constitutes eclampsia. The nonconvulsive type is a diagnosis based on postmortem finding of eclamptic pathology following coma and death in a pregnant woman. Nonconvulsive eclampsia is not a clinical diagnosis.

Vomiting of pregnancy, as suggested by the American Committee on Maternal Welfare, may or may not be a toxemia. The occurrence in pregnancy of persistent vomiting is, per se, a diagnosis. Whether the vomiting is "due to the pregnancy" or just incidental to it is moot and not to be considered here.

The so-called "unclassified toxemias" are those cases which cannot be placed in the proper category during the pregnancy. During the puerperium and with follow-up study or necropsy, these cases will be found to fit into one of the other groups, A or B.

The accurate and proper appraisal of the objective signs in patients is of great value because the exact diagnosis and classification makes it possible to set up the necessary and correct therapeutic regime during the pregnancy and afterward. It makes a more intelligent prognosis available as to future life and as to the possible course of future pregnancies. Proper classification makes available accurate statistics, which are of utmost importance to the acuity and advance of any branch of science.

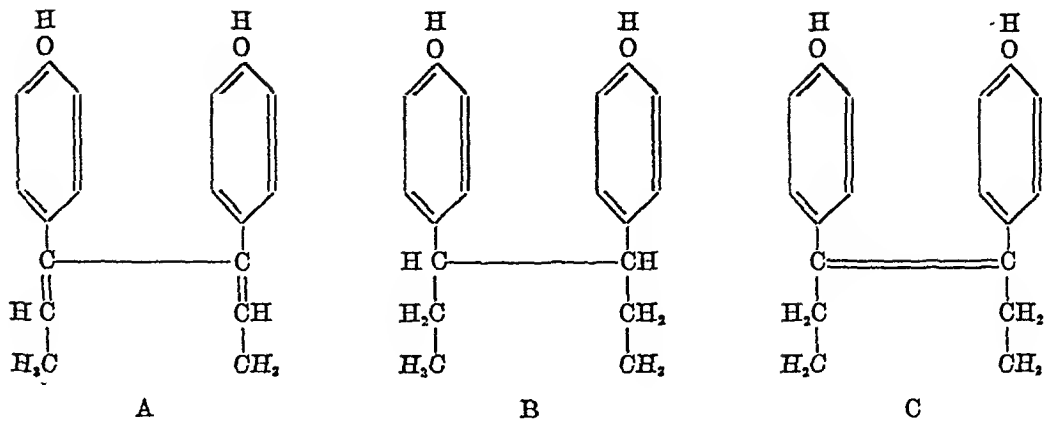
### Summary

1. The classification of the toxemias of pregnancy of the American Committee on Maternal Welfare has been presented and analyzed.

2. Certain objective findings which may serve as points of differential diagnosis of the various toxemias of pregnancy have been pointed out.

3. The necessity for blood chemistry studies and evaluation has been demonstrated, and the inclusion of blood chemistry as a criterion of classification has been suggested.

4. Abandonment of the designations "mild" and "severe" in the classification of pre-eclampsia has been suggested.



### Present Study

This study concerns our experiences in treating a total of 80 clinic and private menopausal patients with orally administered dienestrol.\* Daily doses of the drug ranged from 0.2 mg. to 1.5 mg. according to the severity of the symptoms. Since seven patients were uncooperative (failing to return to the clinic or to adhere to prescribed dosage of medication), our statistics are based on our observations of the therapeutic efficacy of dienestrol in 73 menopausal patients.

The average age of our patients was 48.5 years; the youngest was 32 and the oldest 65 years of age. Thirty-six, or approximately 50 per cent, of these patients had received estrogenic therapy in some form previous to this study.

Our patients complained of the usual symptoms associated with the female climacteric. The causes of these symptoms are tabulated in Table I, and their incidence in this group of patients is listed in Table II. Clinical observations were continued for periods of two to six months.

The efficacy of dienestrol therapy was determined by the effect of the drug on the climacteric symptoms and by vaginal smear examination after the

TABLE I. CAUSES OF CLIMACTERIC SYMPTOMS

Spontaneous menopause	43	(58.9%)
Hysterectomy	16	(21.9%)
Castration	2	( 2.7%)
Radiation	5	( 6.8%)
Premature ovarian failure	7	( 9.5%)
Total	73	(100.0%)

TABLE II. INCIDENCE OF SYMPTOMS

Flashes	63	(87.6%)
Chills and sweats	34	(46.5%)
Irritability	36	(49.3%)
Nervousness	55	(75.3%)
Vertigo	39	(53.4%)
Lack of mental concentration	30	(41.09%)
Mental depression	28	(38.3%)
Sleep disturbances	51	(69.8%)
Headaches	48	(65.7%)
Gastrointestinal disturbances	15	(20.5%)
Generalized vague aches	43	(58.9%)

\*Dienestrol tablets (0.1 mg. and 0.5 mg.) were supplied by White Laboratories, Inc., Newark, N. J.

## A PRELIMINARY EVALUATION OF DIENESTROL IN THE MENOPAUSE

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THE synthesis of stilbestrol by Dodds and his co-workers<sup>1</sup> and the later development of other synthetic estrogenic compounds have caused a widespread interest in the clinical value of these substances. Over a hundred synthetic compounds have been shown to be estrogenic in varying degrees. A large number of investigators have reported on the value of such synthetic compounds, compared with natural estrogens, in the control of menopausal symptoms, in the treatment of senile vaginitis and juvenile vulvovaginitis, and in the suppression of lactation. It has been clearly demonstrated that certain synthetic estrogens are not only as effective as the natural estrogens, but are as therapeutically potent when administered orally as the natural estrogens are when given parenterally.<sup>2-6</sup>

The most desirable estrogen, from a clinical viewpoint, is one that is non-toxic in addition to possessing a potent estrogenic activity that is prolonged in effect. Clinical investigation has shown that the use of the better known synthetic estrogenic compounds is accompanied, more or less, by undesirable side-reactions. Gastrointestinal symptoms are the most frequent untoward reactions noted. Their incidence has been reported to occur in from 6 per cent to 87 per cent of cases treated with various estrogenic substances.<sup>5-9</sup>

### History of Dienestrol

In searching for the ideal estrogen, we undertook to study the clinical effectiveness of the "hexadiene compound" of Dodds, more recently designated dienestrol by the British General Medical Council.

The chemical and physical properties of dienestrol were first reported in 1938 by Dodds and his co-workers.<sup>10, 11</sup> The chemical configuration of dienestrol (A) reveals that it differs from hexestrol (B) and stilbestrol (C) with respect to the number of double bonds (degree of unsaturation) in the molecules. The two double bonds in the substituent side-chains are believed to contribute to the greater biological activity of dienestrol (see graph).

Because of its difficult synthesis, dienestrol has not been made available to clinicians until relatively recently. Emmens,<sup>12</sup> in 1939, showed that when dienestrol was orally administered to mice it had the greatest activity, compared with subcutaneous administration of any of the estrogens examined up to that time. Barnes<sup>4, 13</sup> found this compound, administered orally to human subjects, to be a potent, safe, and nontoxic estrogenic substance. She achieved therapeutic response, in suppression of lactation, with dienestrol in one-tenth the dose required in the case of stilbestrol and hexestrol.

CASE 2.—*Spontaneous menopause*: Miss G. Y., aged 49 years, single. *Complaints*: few hot flushes; pressure on top of head; mild insomnia; vertigo; heaviness of eyes; dryness of skin; alopecia areata; stiffness of legs; paresthesia. *Past history*: no surgery. Previous estrogenic therapy caused aggravation of flushes and uterine bleeding became profuse and clotted. *Examination*: Blood

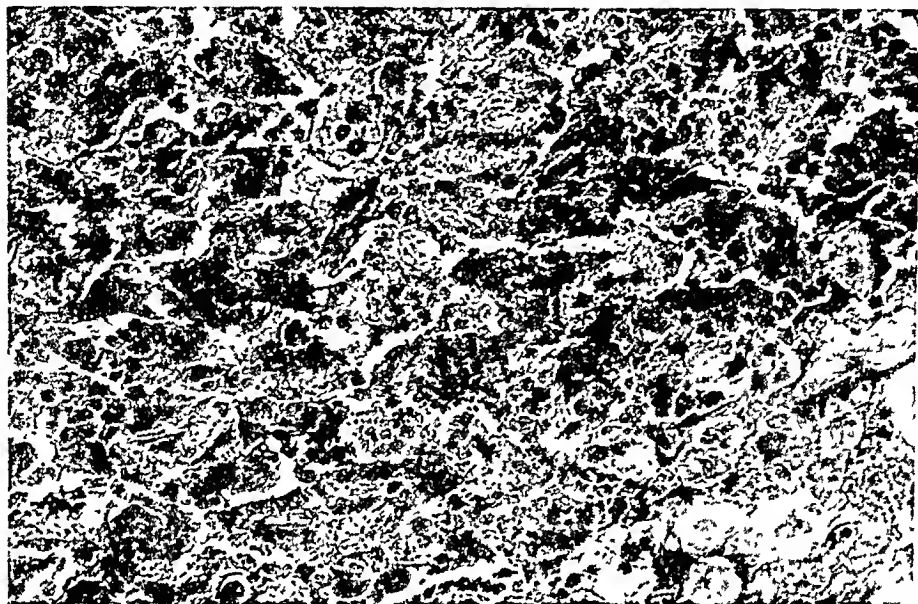


Fig. 1.—Miss G. Y., aged 49 years, 4/29/46. Before therapy—nonestrous phase.

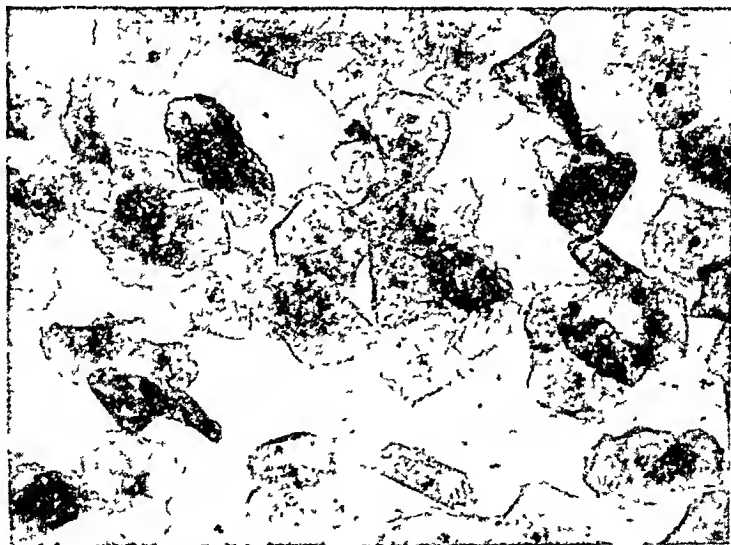


Fig. 2.—Miss G. Y., aged 49 years, 5/18/46. After three weeks' therapy—hyperestrinization.

pressure, 110/60; pulse, 76; basal metabolism rate, plus 5 per cent; weight, 151 pounds. Senile regression of pelvic organs and mucous membranes. *Vaginal smears*: 4/29/46—1-2 plus (nonestrous phase); 5/5/46—2 plus; 5/18/46—5 plus (hyperestrinization phase). (See Figs. 1 and 2.) *Therapy*: One milligram dienestrol daily starting 4/29/46. *Results*: Excellent improvement in all symptoms.

CASE 3.—*Hysterectomy one month previous*: Mrs. B. B., aged 37 years, married, three children. *Complaints*: Hot flushes; perspiration; mastalgia;



TABLE III. RESULTS OF VAGINAL SMEAR EXAMINATIONS

	BEFORE DIENESTROL	AFTER DIENESTROL
Low estrous	23	9
Estrous	22	56
Nonestrous	26	6
Not done	2	2
Total	73	73

method of Papanicolaou and Shorr.<sup>14</sup> Vaginal smear examination was not done in two cases for personal reasons of the patients. Results of vaginal smears are shown in Table III.

### Results of Study

Three (4.1 per cent) of our patients were suffering from other medical complications, such as mental depression, alopecia areata following hysterectomy, and psychoneurosis, and presented no clear-cut indications for estrogenic therapy. No appreciable effect of estrogenic replacement therapy was noted in these patients.

Prompt relief of symptoms was reported by the remaining 70 patients (95.9 per cent). Those who had received previous estrogenic therapy reported that their symptoms were quickly and fully relieved by dienestrol, even though some of these patients had not had complete alleviation of their symptoms by estrogenic preparations previously used. Dienestrol also seemed to effect a sense of well-being, to allay apprehension, and to give patients renewed energy.

Improvement in vaginal smears generally corresponded with the clinical improvement reported. In a few cases clinical improvement was obtained without any marked change in the vaginal smear. In certain other cases, particularly those suffering with various neuroses, there was an improvement in the vaginal smear, although no clinical improvement was reported by these patients, denoting that appropriate dosage of dienestrol had been administered.

*Untoward Effects.*—Of this group of patients, only five (6.8 per cent) complained of pelvic congestion when dienestrol was continued over a long period of time. Two (2.7 per cent) instances of withdrawal bleeding were noted, but in each of these cases the bleeding was very mild and of short duration.

Three of our patients complained of slight nausea during dienestrol therapy. One of these was under concurrent treatment for gall bladder disease, while another stated that she reacts unfavorably to any new medication. Excluding the latter two cases, the incidence of nausea in our series of 73 patients, therefore, was limited to one case (1.3 per cent). This low incidence of nausea is, in our experience and the experience of other investigators,<sup>5-9</sup> in contrast with that encountered during treatment with other synthetic estrogens.

### Case Reports

**CASE 1.**—*Premature ovarian failure:* Mrs. M. H., aged 47 years; married, no children. *Complaints:* hot flushes (20 per day); chills, occasional headaches, especially on first day of period; nervousness; irritability; vertigo; paresthesia of hands; and arthralgia. *Past history:* no serious illnesses; no surgery. *Examination:* Blood pressure, 130/90; pulse, 76; weight, 196½ pounds; heart, negative; no evidence of pelvic pathology. *Vaginal smears:* 5/5/46—2 plus (nonestrous phase); 5/10/46—4 plus (full estrous phase); 5/24/46—4 plus. *Therapy:* One milligram of dienestrol daily initiated 5/5/46. *Results:* Improvement in all symptoms. Slight paresthesia persists.

vertigo; generalized aches; vaginal pruritus. *Past history*: No surgery. *Examination*: Blood pressure, 120/70; pulse, 80; weight, 137¾ pounds; heart, negative; urinalysis, negative. *Pelvic*: Uterus normal in size and position; intra-cervical polyp: senile regression. *Vaginal smears*: 3/6/46—2 plus; 3/20/46—3 plus; 4/9/46—3 plus; 5/14/46—4 plus. *Therapy*: Dienestrol, 0.3 mg. daily, initiated 3/6/46; increased on 3/20/46 to 1 mg. daily. *Results*: Excellent improvement in all symptoms.

CASE 5.—*Spontaneous menopause of two months' duration*: Mrs. R. C., aged 49 years, married, five children. *Complaints*: Irregular periods past year; hot flushes; nervousness; insomnia and headaches; arthralgia. *Past history*: Appendectomy at 22 years of age. Irregular estrogenic therapy (premarin)—none since January, 1946. *Examination*: Blood pressure, 100/60; pulse, 70; weight, 128 pounds; heart, negative; urinalysis, negative. *Pelvic*: cystocele and rectocele. *Therapy*: Dienestrol, 0.3 mg. daily, initiated 4/16/46; gradually increased to 1.5 mg. daily. *Vaginal smears*: 4/16/46—2 plus; 4/30/46—3 plus; 5/20/46—3 plus; 6/10/46—1. plus, 6/24/46—4 plus. *Results*: Excellent improvement in all symptoms.

CASE 6.—*Hysterectomy 12 years ago*: Mrs. P. H., aged 54 years, married, two children. *Complaints*: Hot flushes every half hour (no relief from estrogenic therapy); headaches; left mastalgia; pain in left shoulder; mental depression. *Past history*: Appendectomy and hysterectomy twelve years ago. Hot flushes started three weeks after hysterectomy. *Examination*: Blood pressure 124/80; pulse 84; urinalysis negative. *Pelvic*: senile regression of pelvic organs and mucous membranes. *Therapy*: Dienestrol, 1.5 mg. daily, initiated 5/8/46, decreased on 6/20/46 to 1 mg. daily. *Vaginal smears*: 5/8/46—nonestrous; 5/28/46—4 plus (see Figs. 3 and 4). *Results*: Improvement in all symptoms.

### Comment

Approximately 50 per cent of our patients had received estrogenic therapy in some form previous to this study. This was inadequate either in dosage or in continuity of therapy, since their symptoms were not relieved thereby. Because of this, many of our patients had a vaginal smear which showed a low estrogenic phase at the time dienestrol therapy was instituted.

Daily dosage of dienestrol depended upon the severity of the symptoms. Some patients whose symptoms were not very pronounced were placed on low doses. It is our opinion that for good initial effects, to build up the confidence of the patient, and prove that the symptoms can be controlled, larger doses should be employed in the beginning of therapy but should be quickly reduced to a maintenance dose with periods of interruption of therapy. We have determined, from our series of patients, that a maintenance dose of 0.3 mg. dienestrol daily is ideal. We have noticed that interruption of therapy takes place almost automatically since the patients either forget to take the tablets or are only too glad to discontinue medication when symptomatic relief is obtained. Most of our patients state that they get very weary of swallowing pills and remember them only when symptoms recur.

A large number of our patients lowered the dosage of dienestrol of their own accord, or discontinued it entirely when they were free of symptoms and did not return for recheck until symptoms returned. A few patients claimed they could be maintained on 0.2 mg. daily or 0.5 mg. two or three times weekly.

migraine headaches of three years' duration; mental depression. *Past history:* Ovarian resection and suspension in 1940 followed by hot flushes which gradually became worse. Hysterectomy one month previous to this study. Moderate improvement of symptoms on premarin therapy. *Examination:* Blood pressure, 104/60; pulse, 64; weight, 131½ pounds. Pelvis negative. *Vaginal smears:* 12/11/45—1 plus; 1/5/46—2 plus; 2/1/46—2 plus; 2/14/46—2 plus;



Fig. 3.—Mrs. P. H., aged 54 years, 5/8/46. Before therapy—nonestrous phase.



Fig. 4.—5/28/46. After 20 days' therapy—full estrous phase.

2/19/46—3 plus; 3/1/46—3 plus; 5/27/46—1 plus. *Therapy:* Premarin was discontinued and dienestrol started in 1 mg. daily doses on 12/11/45. *Results:* There was a gradual improvement in vaginal smears and dosage was decreased to 0.3 mg. and later to 0.2 mg. of dienestrol daily. Good results were maintained on 0.3 mg. daily. Some symptoms recurred on 0.2 mg. daily. Patient still complained of neuralgia and thiamine chloride was added on 3/1/46. Dienestrol was increased to 0.5 mg. daily and best results obtained. On decreasing dosage of medication the quality of the vaginal smears decreased.

CASE 4.—*Spontaneous menopause.* Mrs. E. Q., aged 51 years, married, two children. *Complaints:* hot flushes, worse at night; insomnia; headaches;

## DYSGERMINOMA OF THE OVARY

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**T**WO cases of dysgerminoma of the ovary are reported herewith. One is of interest because of the association of dysgerminoma with a normal pregnancy; the other because of normal menstruation associated with dysgerminoma in the presence of marked underdevelopment of the internal genital organs.

**CASE 1.**—A 21-year-old white woman, admitted, August, 1944, to the Oakland Regional Hospital, with the chief complaint of constipation of two and one-half months' duration, amenorrhea of two months' duration, and a symptomless mass in the abdomen first noticed on June 22, 1944, approximately two months previously.

Past history showed that menstruation began at the age of 12 years and recurred every thirty-five days. Duration was four days; amount of flow was normal. Last menstrual period occurred June 7, 1944, two months prior to admission. Early in June, 1944, the patient first began to notice constipation. This condition became steadily worse until the time of admission, when cathartics and enemas were required. The mass in the abdomen was first noticed by the patient about June 22, 1944. There was no associated pain or tenderness. Increased urinary frequency and nocturia had been noticed in the last few weeks. The patient came to the hospital because she thought her symptoms were due entirely to pregnancy. She had gained ten pounds in the month prior to admission.

Physical examination showed a well-developed, well-nourished young adult white woman who did not appear ill. Secondary sex characteristics were entirely normal. The abdomen showed a midline mass which appeared to arise from the pelvis. It measured 22 cm. above the symphysis pubis. The mass was smooth, freely movable, and gave the impression of being cystic. It was not tender.

Pelvic examination showed the cervix was soft and of a congested, slightly purplish color. The body of the uterus could not be definitely outlined. A large mass was palpated in the cul-de-sac of the pelvis. Remainder of the examination was normal. Admission diagnosis was that of a large ovarian cyst.

X-ray studies of the abdomen revealed a large, soft tissue mass arising from the right side of the pelvis and extending up to L-3 (Fig. 1). Intravenous urogram showed dilatation of the right calyces, kidney, pelvis, and proximal ureter with displacement of the right ureter to the left (Fig. 2). The left side was normal. Barium enema showed a slight pressure deformity of the proximal rectum, with lateral and upward displacement of the ascending colon and cecum. The mass did not appear to be attached to the bowel. Small bowel study and chest plate were normal.

Laboratory studies showed the following: red blood cells, 3,490,000; white blood cells, 6,500; hemoglobin, 71 per cent. Urinalysis—negative; Kahn—negative; Friedman test—positive on two occasions.

Repeated pelvic examination showed the coexistence of two separate masses, one of which was then assumed to be a large ovarian cyst, and the other a normal pregnancy of about three months' duration. Exploratory laparotomy was performed through a lower right rectus muscle splitting incision. The uterus was found to be enlarged to the size of a three and one-half month pregnancy. A large, freely movable nodular mass was found lying on the right side of the abdomen and attached to the right broad ligament by a definite pedicle. The

It has been our experience that the more systematic the regime of estrogenic therapy, the better and more uniform is the response.

### Conclusions

1. Orally administered dienestrol gave prompt symptomatic relief in 70 menopausal patients in whom estrogenic replacement therapy was clearly indicated. Vaginal smear response to treatment generally corresponded with symptomatic improvement.

2. The unusually low incidence of gastrointestinal intolerance (1.3 per cent) and the absence of other toxic side effects make this preparation particularly commendable.

3. Dienestrol is a potent, safe, and unusually well-tolerated synthetic estrogenic substance.

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35 LESLIE STREET

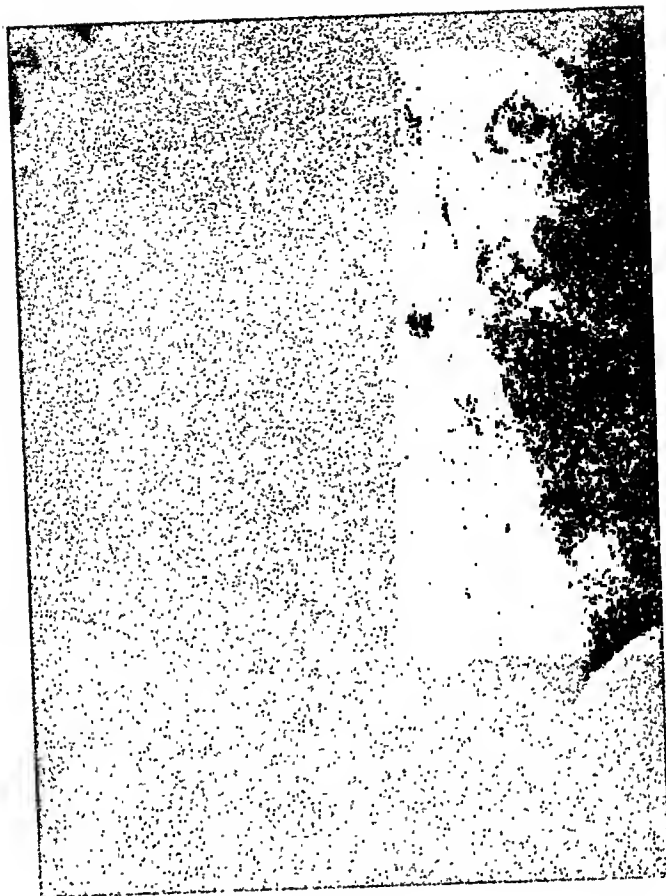


Fig. 2.

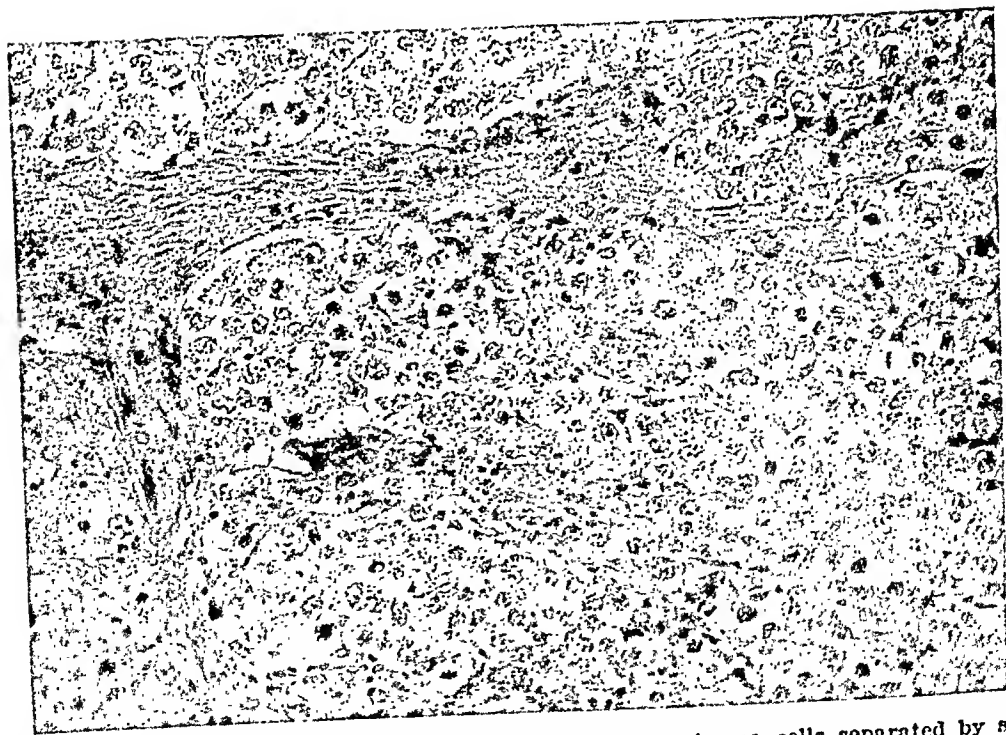


Fig. 3.—Photomicrograph shows nests and cords of carcinoma cells separated by strands of fibrous tissue. Numerous typical and atypical mitotic figures can be seen and a moderate lymphocytic infiltration is present in the fibrous tissue septa. An occasional tumor giant cell is seen throughout the section.

tumor seemed to be a solid ovarian tumor. It was removed intact after ligating the pedicle. Further abdominal exploration was unrevealing, the left ovary and tube being normal in appearance.

Postoperative convalescence was uneventful. The patient was discharged on the thirteenth postoperative day. Radiation therapy was deemed inadvisable.

*Pathologic Description.*—Specimen consisted of an ovarian mass which was entirely encapsulated and measured 19 by 13 by 11 cm. It was attached to a small pedicle which measured approximately 2 cm. in diameter. The general contour of the mass was somewhat kidney-shaped and slightly nodular. On section, it cut with ease. However, the mass seemed to be composed of solid tissue



Fig. 1.

which was gelatinous, edematous, and brainlike in consistency. There were small scattered cystic areas up to 1 cm. in diameter throughout the entire tumor, and in some areas there was hemorrhagic extravasation into the tissues. Microscopically (Fig. 3), this tissue was composed of nests, masses, and cords of large cells which had a granular and vesicular nucleus and a clear cytoplasm with a well-defined cell margin. The cells varied somewhat in size. There were numerous typical and atypical mitotic figures present. Tumor giant cells were seen throughout the sections. There was a delicate framework of fibrous tissue coursing throughout the sections, and this fibrous tissue was moderately infiltrated with lymphocytes. There was also infiltration of lymphocytes between the groups of malignant cells. Some sections showed large areas of necrosis.

*Diagnosis:* Dysgerminoma of the ovary. The patient moved to another section of the country and was not contacted for some time. She was delivered of an 8 pound, 6 ounce baby girl without complication on March 8, 1945. Ex-



negative; Friedman test—negative. The patient ran a low-grade temperature and was treated on admission for an acute upper respiratory infection. This subsided, but the fever persisted and was then ascribed as being due to degenerative changes within the tumor.

On Dec. 21, 1945, a celiotomy was performed through a subumbilical midline incision. An almost solid lobulated mass about the size of a child's head was found in the right lower portion of the abdomen. On its surface was a considerable quantity of grayish-white partially organized fibrous exudate. In the process of delivering the mass from the abdomen a large cystic area was opened allowing a considerable quantity of serosanguineous fluid to escape within the abdominal cavity. The tumor was attached to the right broad ligament by a broad thick vascular pedicle. Adhesions existed between the tumor and the pelvic floor. These were freed with blunt dissection without penetrating the capsule. The pedicle was transfixed and ligated, and the tumor removed. The entire pelvic floor was thickened, due, undoubtedly, to organization of inflammatory exudate. The left ovary was not present. Only a small lateral fimbriated portion of a maldeveloped left tube could be demonstrated. In the midline where the uterus would normally be present, one could feel retroperitoneally a thickened mass about 5 cm. in length and of about the diameter of a lead pencil, which probably represented a rudimentary uterus. Further abdominal exploration was unrevealing. The patient's postoperative course was uneventful.

*Pathologic Description.*—Specimen consisted of an ovarian mass measuring 21 by 14 by 10½ cm. This mass was well encapsulated except for a one-half centimeter in diameter perforation at one end of the tumor from which necrotic material could be expressed. Over the lower end of the tumor the capsule is covered with a grayish-white exudate which represents organized fibrin. The rest of the capsule is smooth and glistening and contains large veins coursing through it. On section, the tumor mass cuts with ease, exposing a large central degenerative cyst measuring 5 cm. in diameter, which is filled with necrotic material, blood clot, and serous fluid. There are numerous areas of cystic degeneration up to 1½ cm. in diameter scattered throughout the tumor. In some places, there is marked hemorrhagic extravasation into the tumor tissue. Between the cystlike areas of degeneration the typical appearance of the tissue is pearly gray, soft, friable, and brainlike. Attached to this ovarian mass is a Fallopian tube which measures 8½ by .8 cm.

Microscopically, sections through various portions of the tumor (Fig. 4) revealed the tissue to be very cellular with scant fibrous tissue interspersed at regular intervals. The cells were arranged in masses, nests, and cords. In some areas there was an attempt at granular formation. The cells were large, round, and polygonal. They had clear cytoplasm with well-demarcated cell margins. The nuclei were large, vesicular, and stained heavily with hematoxylin. Numerous typical and atypical mitotic figures were seen. Sections taken from the periphery of the tumor were very cellular and well preserved. Sections taken closer to the center of the tumor showed large areas of degeneration and necrosis. Other sections showed large areas of hemorrhagic infiltration into the tumor tissue. The capsule showed a marked infiltration of polymorphs, plasma cells, and the laying down of fibrin. There was no infiltration of tumor tissue into the capsule. There was moderate lymphocytic infiltration into the sparse fibrous connective tissue coursing throughout the sections. Diagnosis: Dysgerminoma of the ovary, with marked degenerative changes.

The patient was transferred to a general hospital for deep x-ray therapy. The authors were able to communicate with the patient on April 18, 1946. She had various complaints of an unspecific nature, but nothing to indicate that there had been a recurrence of the tumor.



amination of the patient April 12, 1946, revealed that her physical condition is entirely normal in all respects. There is no evidence of recurrence or metastasis of the tumor approximately two years after its removal.

CASE 2.—A 22-year-old white woman, a WAC, was admitted Nov. 27, 1944, with a chief complaint of soreness and tenderness in the right lower quadrant, abdominal mass in that area, and moderate constipation.

Past history was as follows: Menses began at 14 years of age; regular every twenty-eight days; normal in amount; two to three days' duration. Last menstrual period had occurred thirty-one days prior to admission. No recent weight loss was noted.

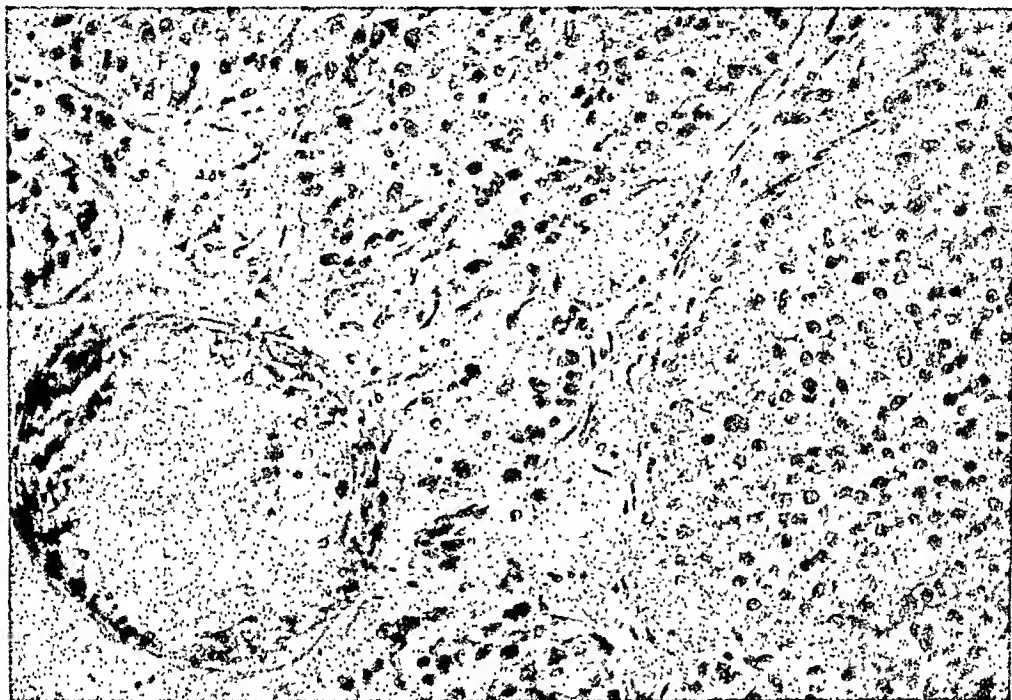


Fig. 4.—Photomicrograph shows large carcinoma cells arranged in nests and cords with a sparse and delicate fibrous tissue stroma separating the nests of cells. Moderate lymphocytic infiltration can be seen in this connective tissue. The lower margin of the section shows a small blood vessel which is apparently lined by some large carcinoma cells and has a few malignant cells in the lumen.

About two weeks prior to admission, the patient bumped the abdomen against the framework of a truck. The injured area remained sore for several days. Three days following the injury she noticed a mass in the lower abdomen which was tender on pressure. For four days prior to admission she had had no bowel evacuation.

Physical examination revealed a young white woman who did not appear ill. The body build was definitely masculine, with poorly developed breasts and a narrow pelvis. Hirsutism was of normal feminine type. There was a mass in the lower abdomen which seemed to arise from the right side of the pelvis. It filled the right lower portion of the abdomen to the level of the umbilicus and gave the impression of being cystic to palpation. Pelvic examination was unsatisfactory because of an intact hymen. Rectal examination showed the true pelvis to be empty. No uterus or cervix could be palpated. The external genitals were of normal female type. Remainder of the examination was entirely negative.

Laboratory investigation showed the following: red blood cells, 3,610,000; white blood cells, 10,750; hemoglobin, 75 per cent; sedimentation rate, 101 mm. in one hour, 125 mm. in two hours. Urinalysis was essentially negative. Kahn—

180/100. The chief complaint was irregular vaginal bleeding of thirty-six months' duration. There had been no definite amenorrheic phase of the menopause, but she had experienced flushes and sweats occasionally. In June, 1945, she began to grow reddish brown hair on the lips, chin, cheeks, chest, and extremities. Her skin, formerly normal, began to have a flushed appearance, and soon acne of the face, chest, and shoulders occurred. Her voice became husky and she had to give up singing, a definite handicap to her as a leader of church activities. Previously frigid, she began to experience orgasms for the first time in her married life of twenty-six years.

Examination of the head and neck revealed a florid rotund face and the acne described by the patient. The facial lesions were mostly cicatrized. The cheeks, chin, lips, neck, shoulders, and extremities were covered with reddish brown hair of medium texture, which on the exposed surfaces had been altered by bleaches and pumice stone. The breasts were rather small in proportion to the obesity of the patient.

Extreme obesity handicapped the examination of the abdomen. An irregular, firm, painless tumor of indeterminate size occupied the suprapubic region. The clitoris was enlarged to 3.5 by 1.5 cm., and was quite erectile. When erect the distended corpora cavernosa gave the dorsum a grooved appearance. The mucosa of the vestibule and the vagina was definitely atrophic. The cervix showed a few retention cysts, but was otherwise normal except for fixation. The corpus uteri was enlarged to the total bulk of about a ten weeks' pregnancy by two or more discrete nodules. It was mobile without discomfort. The adnexa could not be satisfactorily outlined on account of the obesity of the patient. Blood count was normal. Urinalysis showed trace of albumin and sugar and an occasional hyaline cast.

Impression was (1) fibromyomatous uterus and (2) virilism with acne and hypertension which suggested extragenital origin, possibly pituitary basophilism, etc. It was decided that the patient should have total hysterectomy because of the possible coexistence of adenocarcinoma of the corpus uteri.

Laparotomy was performed Jan. 15, 1946. The uterus was fairly symmetrically enlarged but nodular in consistency. The largest discrete nodule described preoperatively was found to be a solid tumor of the left ovary about 4 cm. by 3 cm. by 4 cm. The capsule was smooth and glistening, through which could be seen lobulated orange-yellow material. The right ovary and both tubes were of normal postmenopausal type. The cervix was fixed by thickened cardinal ligaments. Total hysterectomy and bilateral salpingo-oophorectomy were performed.

Convalescence was normal and rapid and the wound healed primarily. By the eighth day the acne was improving and the hypertension had disappeared, the blood pressure being 130/80. The patient was transferred to her home on the tenth postoperative day.

*Pathological Report.*—(Dr. Everett L. Bishop). The specimen consisted of a large uterus with the cervix and adnexa. The cervix showed a few small cysts, and the canal was filled with mucus. The uterus was 8 cm. in diameter, the enlargement due to several fibromyomas, one of which was 4.5 cm. in diameter and compressed the uterine mucosa. The endometrium was atrophic, and there was an area of organized hemorrhage where it was compressed by the tumor as described. There were several smaller fibrous tumors scattered throughout the myometrium. The Fallopian tubes were grossly normal. There was one small hydatid cyst.

The right ovary was very sclerotic, measuring 3.5 by 1.5 by 1 cm. The left ovary measured 5 by 5 by 3 cm., had a smooth capsule, and cut surface

## ADRENAL-LIKE MASCULINIZING TUMOR OF THE OVARY ASSOCIATED WITH BLEEDING FIBROMYOMA UTERI

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THE literature on adrenal-like tumor of the ovary is limited by the paucity of material and is complicated by marked diversity in nomenclature and classification. The tumor is variously called adrenal tumor, adrenal carcinoma, adrenal cortex carcinoma, hypernephroma, hypernephroid tumor, interstitioma, lipoid-cell tumor, and luteoma of the ovary. Rottino and McGrath<sup>1</sup> have coined the etymologically objectionable Latin-Greek hybrid "masculinoblastoma" which is only clinically descriptive. The masculinization syndrome produced by these tumors must be distinguished from that due to pituitary basophilism or to androgenic tumors arising from the adrenal gland itself instead of the ovary.

Barzilai,<sup>2</sup> in 1943, stated that less than ten cases of what he chose to call "virilizing lipoid cell tumor of the ovary" had been described. He also stated that "one and the same tumor has occasionally been described under different names." Kepler, Doekerty, and Priestly<sup>3</sup> exhaustively reviewed the literature on adrenal tumors of the ovary in 1944, collecting thirteen cases to which they added one of their own. Since then four additional cases have been reported.<sup>4-6</sup> The ages of the patients varied from 15 to 62 years, and all of them had amenorrhea. No mention was made of the coexistence of fibromyoma uteri in any case, but one was associated with bilateral dermoid cysts of the ovary. Hypertension was present in four of six cases, and not mentioned in ten. Obesity was pronounced in eight cases. All patients had masculine hirsutism in some degree, and eleven of thirteen had voice changes. Hypertrophy of the clitoris was present in ten of the twelve cases in which the organ was described.

Glycosuria existed in six of eleven cases in which the urinalysis was noted. Four individuals had definite tendency toward polycythemia vera. Hormone studies were seldom made, but usually showed elevated androgens and diminished gonadotropins and estrogens.

The masculinization syndrome was completely cured in four patients, one of which later had a normal pregnancy. Virilism was improved to some degree in seven other cases. Vaginal bleeding occurred for the first time in sixteen years on the ninth postoperative day of a patient who died two days later. One patient died at operation, and another died of recurrence after four years.

The right ovary was involved in eight cases and the left in seven, while in one case the tumor was bilateral. The tumor varied in size from microscopic dimensions to 15 cm. by 14 cm. by 9 cm. A definite capsule existed in all cases described and ovarian origin of the tumor was identified in all. The cut surface of the tumor was of yellow to orange color in all tumors described, most of which were said to be slightly lobulated.

### Case Report

The patient, aged 54 years, white, gravida iii, para iii, was admitted to Crawford W. Long Hospital Jan. 9, 1946, and discharged Jan. 25, 1946. She was 62 inches in height and weighed 200 pounds. Her blood pressure was

### Summary

A short review of the literature on the adrenal-like tumor of the ovary with masculinization syndrome is given. A case is reported which is the only one in literature which was associated with vaginal bleeding of any kind, this bleeding being due to fibromyoma uteri compressing atrophic endometrium. The tumor was apparently benign, and the patient was markedly improved by operation.

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showed a solid mass of brilliant, orange colored, moderately firm, but not hard tissue without necrosis or hemorrhage.

*Microscopic:* Sections of the cervix showed the usual fibromuscular structure with active glands and numerous cysts, some of which were filled with mucus. Sections of the uterus showed a diffuse fibrosis of the muscle. The fibromyomatous tumor showed no degenerative changes. The endometrium was thin and atrophic with intact surface epithelium and a few glands of medium and small size. There was a large area of hemorrhage into the endometrium, but no ulceration. Sections of the small right ovary showed a very dense sclerotic structure without follicles or cysts. Sections of the larger ovary showed only a narrow covering layer of identifiable ovarian tissue in which were numerous congested vessels, several large cells containing dark brown pigment, but no follicles or cysts. The bulk of the mass was composed of a broad sheet of large, faintly granular, lipoid type of cells with very little supporting connecting tissue, but with numerous blood vessels of various sizes. In a few places some of the cells were smaller with more opaque and granular cytoplasm. There was an occasional small area of hemorrhage, but no necrosis. There were no giant cells of any type.



Fig. 1.—Section of tumor and capsule of ovarian tissue.

*Pathologic diagnosis:* Adrenal tumor of ovary; multiple fibromyoma of the uterus with infarction of atrophic endometrium.

At the follow-up examination twelve weeks after operation, the patient was apparently well. Her weight had decreased to 178 pounds, the blood pressure was 140/83, and the urine was normal. The voice was slightly improved, but the patient still could not risk singing in public. The hirsutism was much improved; the hair on the chest, shoulders, and extremities had largely disappeared, despite the patient not having used a depilatory or pumice stone since the operation. The facial hirsutism was still present but in a markedly lessened degree. The acne had entirely disappeared. The clitoris was slightly smaller.

Comment

It is evident from these observations that penicillin is readily absorbed through the vaginal mucosa and appears in the blood in high therapeutic levels. The method is painless. The suppositories are well tolerated and can be administered by the patients themselves. No untoward local or systemic toxic effects were observed. Absorption from the vagina was found to be somewhat slower and more prolonged than absorption after intramuscular injection (Table I).

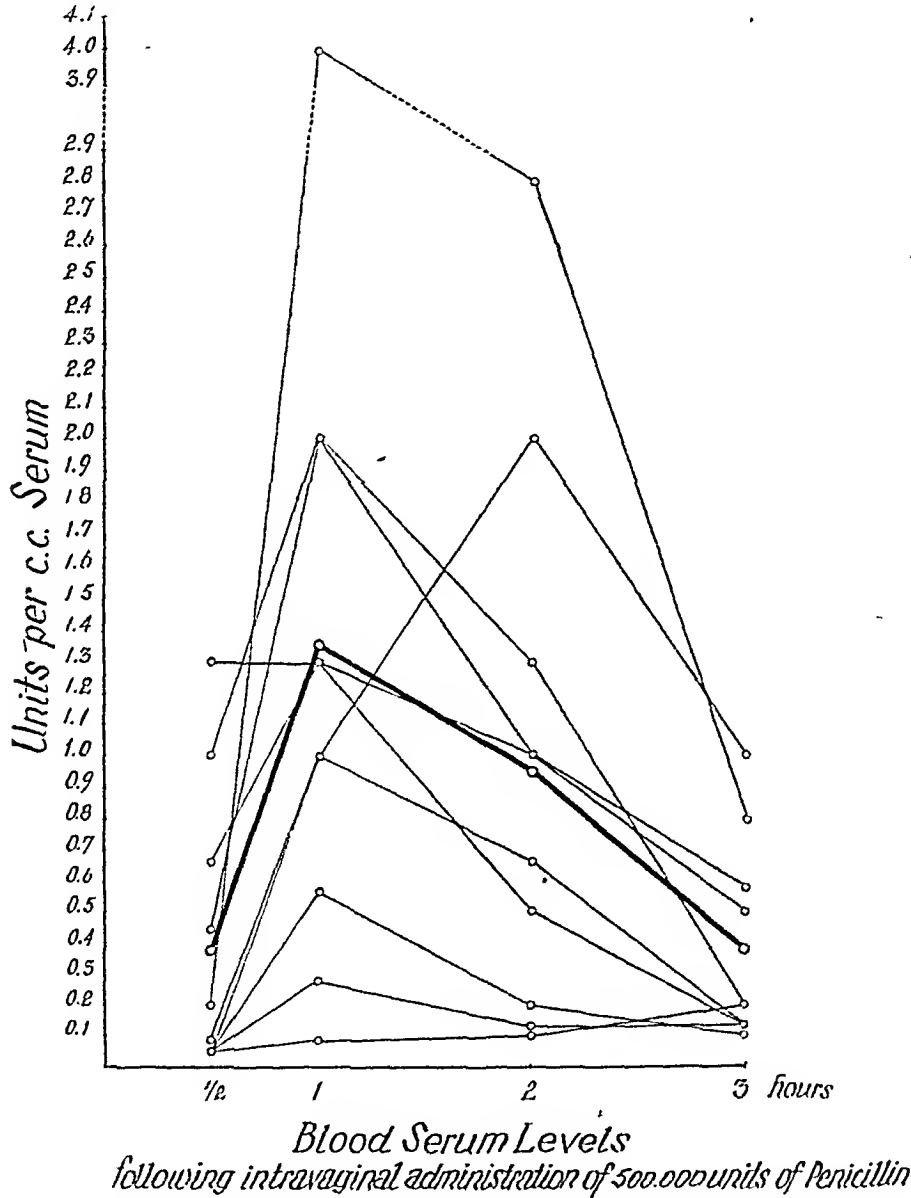


Fig. 1.—Blood levels of penicillin after intravaginal administration of 500,000 units. The heavy line indicates the average.

By the latter method the highest serum levels are achieved in approximately twenty to thirty minutes, whereas after intravaginal administration the maximum is obtained after one hour. Therapeutic levels of penicillin were maintained up to three hours in all cases. It may therefore be possible to use the vagina as a depot from which continuous absorption of penicillin may be achieved. Further studies are in progress to determine the blood levels attained by the use of smaller doses at various intervals.

## ABSORPTION OF PENICILLIN FROM THE VAGINA

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(From the Gynecological Service of the Mount Sinai Hospital)

WE WISH to report briefly the blood levels and urinary excretion of penicillin following the administration of single large doses by the vaginal route. Available literature contains no information on this method of administering penicillin,<sup>1</sup> yet such information is a necessary preliminary to the use of the drug in the local infections commonly encountered in obstetrics and gynecology.

Ten patients on the Gynecological Service were selected for this study. Seven were normal menstruating women, two had had the menopause, and one had had three months of amenorrhea in consequence of an endocrine disorder associated with virilism. Vaginal and cervical infections and other local lesions were absent in all cases. After a vaginal douche of sterile water, five suppositories of calcium penicillin in a base of cocoa butter were placed in the vagina at one time. Each suppository contained 100,000 units of penicillin. In each case the pH of the vagina was determined before and after treatment by means of the Beckman pH Meter, Laboratory Model. For the determination of penicillin in the blood, a modification of the Rammelkamp method was employed, *Staphylococcus aureus* strain H being used as the test organism. Urinary excretion studies were done for twenty-four hours after treatment.

After the intravaginal administration of 500,000 Oxford units the average penicillin level in the blood was 0.38 units per c.c. of serum at the end of thirty minutes; 1.35 units per c.c. at the end of one hour; 0.96 units per c.c. at the end of two hours; and 0.38 units per c.c. at the end of three hours. Wide individual variations were observed which may in part be due to leakage from the introitus (Fig. 1).

Before treatment, the pH of the vagina varied between 4.1 and 7.0. Five hours after treatment the pH varied between 6.3 and 7.5. In a control series of five women treated with plain cocoa butter suppositories, vaginal pH was unchanged after five hours. The total urinary excretion of penicillin in twenty-four hours varied between 33,425 units and 142,000 units, the average being 91,957 units.

TABLE I. BLOOD LEVELS ATTAINED BY VARIOUS METHODS OF ADMINISTRATION

AUTHOR	ROUTE	DOSAGE (UNITS)	LEVELS AT THE END OF			
			½ HR.	1 HR.	2 HR.	3 HR.
Herrell et al <sup>3</sup>	Intramuscularly	50,000		0.96		0.06
Romansky and Rittman <sup>4</sup>	Intramuscularly (beeswax-peanut oil)	66,400		0.039	0.078	0.078
	Intramuscularly	85,000	0.625	0.31	0.15	0.039
Schwartzman <sup>5</sup>	Intramuscularly	100,000	2-6	0.6-4.0	0.1-2.0	0.04-0.8
Gerber et al <sup>6</sup>	Intramuscularly	100,000	6.6*	2.5	1.0	
	Intramuscularly	200,000	11.4*	4.3	1.2	
	Intramuscularly	300,000	16.0*	9.5	2.3	
This Study	Intravaginal	500,000	0.38	1.35	0.96	0.38

\*Twenty minutes.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Cesarean Section

Perez, Manuel Luis, and Echevarria, Ramon: Prophylactic Sulfonamide-Penicillin Therapy in Unclean Operative Obstetric Cases (Cesarean Section), *An. brasil. de ginec.* 21: 339-349, 1946.

The authors have previously shown the beneficial effects of local sulfonamide therapy when performing hysterectomies in unclean cases, as a prophylactic measure against mortality and morbidity. They now report twenty-five cervical cesarean sections, seventeen of which were definitely unclean in which penicillin was used with the sulfonamides. There were no deaths in this series, and the morbidity decreased from the previous incidence of 47.8 per cent to 12 per cent. With few exceptions, 4 Gm. of sulfonamide were implanted intraperitoneally, and 200,000 units of penicillin were given by the intramuscular route. Hence, the addition of penicillin to the sulfonamides were a distinct help.

J. P. GREENHILL.

### Endocrinology

Weaver, John D.: Estrogenic Hormones, Often Only a Psychotherapeutic Agent, *South. M. J.* 39: 581, 1946.

Severe criticism is leveled against the indiscriminate use of the estrogenic hormones. The author has administered peanut oil with and without the estrogenic hormones and obtained equally good results in the relief of symptoms at the climacteric. Use of the estrogens should be restricted to the treatment of gonococcal vulvovaginitis, senile vaginitis, hypoplasia of the uterus, postpartal breast engorgement, some types of habitual abortion, and for its effect upon ovulation.

Circumstantial evidence is presented to indicate that long-continued administration of the estrogens may be carcinogenic. The physician who administers the estrogens without first doing a pelvic examination is sharply criticized.

WILLIAM BICKERS.

### Endometriosis

Couri, A. A., and Ramos, A. N.: Urogenital Endometriosis, *An. brasil de ginec.* 11: 27-33, 1946.

The authors report a case of endometriosis of the bladder which had its origin in the female genitals. In spite of a hysterectomy with removal of the adnexa, the patient's symptoms were not relieved. In fact, they became worse. Examination of the bladder revealed an endometrioma on the anterior wall which had grown inward from the uterine wall. This is the first report of genital endometriosis with bladder involvement reported of genital endometriosis with bladder involvement reported in Brazil.

J. P. GREENHILL.

### Ectopic Pregnancy

Campos da Paz Fo, A.: Hysterosalpingography in the Diagnosis of Ectopic Pregnancy, *Obst. y ginec. latino-am.* 3: 704-712, 1945.

The author is opposed to the use of hysterosalpingography for the diagnosis of tubal pregnancy because he believes the radiologic findings are not characteristic. Analyzing the



TABLE II

CASE	AGE (YEARS)	RACE	MENSES	DIAGNOSIS	GRAVID ITY	PRE R* pH	5 HR. POST R* pH	BLOOD SERUM LEVELS OF PENICILLIN EXPRESSED IN OXFORD UNITS PER C.C.			
								½ HR.	1 HR.	2 HR.	3 HR.
R. B.	21	Negro	Normal	Fibroid	0	4.7	6.5	0.08	1.0	0.66	0.13
R. K.	50	White	Postmen- opause	Fibroid uteri	2	6.5	7.5	0.66	1.3	1.0	0.5
B. S.	42	White	Normal	Cysto- recto- cele	2	4.9	6.3	0.44	2.0	1.0	0.57
R. W.	39	Negro	Normal	Fibroid uteri	3	5.4	6.3	0.55	0.08	0.1	0.2
M. C.	34	Negro	Normal	Fibroid uteri	0	7.0	7.5	0.05	0.27	0.13	0.13
S. F.	39	White	Normal	Fibroid uteri	0	4.1	7.0	1.0	2.0	1.3	0.20
B. Y.	31	White	Amenor- rheic	Virilism	4	6.3	7.0	0.05	0.57	0.2	0.1
L. J.	45	Negro	Normal	Fibroid uteri	1	5.6	7.5	0.05	1.0	2.0	1.0
L. K.	31	White	Normal	Ectopic preg.	4	7.0	7.5	1.3	1.3	0.5	0.13
A. R.	49	White	Postmen- opause	Fibroid uteri	4	5.0	6.5	0.2	4.0	2.7	0.8

\*R equals treatment.

TABLE III. URINARY PENICILLIN EXCRETION

3 HOURS		21 HOURS		TOTAL NO. UNITS EXCRETED IN 24 HR.
VOLUME (C.C.)	UNITS PER C.C.	VOLUME (C.C.)	UNITS PER C.C.	
500	200	1,050	1.0	101,050
350	200	800	13	80,400
750	100	1,200	10	87,000
350	50	1,400	27	55,300
600	100	675	4	62,700
150	270	225	13	33,425
280	270	1,400	27	109,400
250	400	1,025	20	120,500
200	400	1,400	27	127,800
325	400	600	20	142,000

### Conclusions

1. Penicillin in the form of suppositories is readily absorbed through the vagina.
2. Therapeutic levels are easily attained and maintained for at least three hours.
3. This method warrants clinical trial and may prove to be the method of choice for the administration of penicillin in the adult female.

We wish to express our appreciation to the Schenley Laboratories for the Penicillin used in this study.

### References

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3. Romansky, M. J., and Rittman, G. E.: Science 100: 196-198, 1944.
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5. Gerber, I. E., Schwartzman, G., and Baehr, G.: J. A. M. A. 130: 761-764, 1946.

cases. This frequency was much more than was suspected. Tuberculosis of the endometrium was found in 6 per cent of the sterility cases, even in the absence of all palpable evidence of tubal inflammation. Hence, the authors emphasize that, in so-called essential sterility cases where the menstrual cycle is normal, one must think of tuberculosis.

An endometrial biopsy is indispensable in a gynecologic examination where there is chronic palpable inflammation of the uterine adnexa. The discovery of tuberculosis can readily be made in this way and will lead to early treatment.

The authors insist that every piece of tissue removed by curettage, whether it follows therapy for bleeding for a gynecologic condition or an abortion, be examined routinely. This procedure will permit discovery of tuberculosis in cases where it is not suspected.

J. P. GREENHILL.

De La Osa Garces, Leon Lopez: The Use of Penicillin Solution in Cases of Cervicitis, *Tokoginecologia Practica* 5: 226-239, 1946.

The author applied penicillin locally in cases of cervicitis both in the form of a paste and in the form of a solution. The results were so good that he recommends this form of therapy.

J. P. GREENHILL.

### Gynecologic Operations

da Silva Pereira, J. M.: Prolapse of the Female Urethra. Report of Three Cases, *Obst. y ginec. latino-am.* 3: 848-864, 1945.

Prolapse of the urethra—that is to say hernia of the urethral mucosa through the meatus—is a rare affection which is more frequently observed during childhood and after the menopause.

The author proposes the following classification: first degree prolapse: descent of one of the walls only; second degree prolapse: descent of the distal segment of the urethra; third degree prolapse: descent of both the distal and proximal segments.

The symptomatology is changeable, the most frequent disorders being urinary disturbances, pain, and loss of blood. The principal factors which help to make the diagnosis are analyzed, and the technique of a repair operation is described. The latter consists in: (1) transverse hemisection of the tumor down to the meatus, leaving a mark in every corner of the incision; (2) excision of the upper half and suture of the margins with separate stitches, using thin chromic catgut; (3) excision of the inferior part of the tumor. The last stage is the same as for perineorrhaphies.

The purpose of this intervention is to reduce the orifice of the meatus, in order to prevent recurrence or urinary incontinence.

The prognosis, as a rule, is good, the complications being urethral stenosis and incontinence of urine.

J. P. GREENHILL.

Cirio, C. R.: Myometrectomy. Its Conception, Anatomy, Physiology, Technic, Indications and Results, *Obst. y ginec. latino-am.* 3: 761-778, 1945.

According to the author, myometrectomy is the most recent technical advance among the menstruation-preserving operations, and the only one that permits the radical extirpation of all the small, invisible, and impalpable nodules situated in the myometrium. Like any other menstruation-preserving technique, it should not be performed after the forty-eighth nor before the fortieth year of life, and if exceptionally it is to be done on women under 40 years it should be reserved for women who have fulfilled their maternal obligations.

The size of the new menstruating organ is that of an infantile uterus and in some cases even smaller, owing to extirpation of the myometrium, that allows a more perfect final peritonization, and consequently a better recovery than other menstruation-preserving operations.

findings of several authors who have used the method he emphasizes the variety of x-ray pictures described by them. He criticizes the so-called "lacunar image" which is observed in ectopic pregnancies only exceptionally; however, he presents one such case of his own. He also presents several hysterosalpingograms made to test tubal patency in sterility cases, which show pictures identical to those observed by several authors during tubal abortions, and described as "lacunar images"; in the author's opinion they represent the contrast medium spreading into the peritoneal cavity. Based on this observation, he emphasizes the need for taking several pictures. He establishes a difference between a "permanent picture" and a "transitional picture." In discussing the dangers of the hysterosalpingography in the diagnosis of tubal pregnancy, he reports a case in Dr. A. Sarmiento's private practice in which rupture of the tube occurred at the exact moment an exploration was performed.

J. P. GREENHILL.

Weyeneth, R.: Simultaneous Pregnancy in Both Tubes, *Monatsehr. f. Geburtsh. u. Gynäk.* 120: 129-140, 1945.

A case of simultaneous bilateral tubal pregnancy, probably of the same age, is reported by the author. On the right side a rupture of the tube occurred with profuse bleeding into the peritoneal cavity, while on the left side the tubal abortion had taken place with the formation of a tubal hematoma. The etiology was most likely postpartum endometritis and endosalpingitis. This is the seventy-first case of simultaneous bilateral extrauterine pregnancy reported in the literature.

J. P. GREENHILL.

## Gynecology

Dionisi, H., and Ferraris, L. V.: Struma Ovarico With Hyperthyroidism, *Obst. y ginec. latino-am.* 3: 797-811, 1945.

The case of a patient with "struma ovarico," presenting the typical signs of hyperthyroidism and a basal metabolism oscillating between plus 37 and plus 54, is presented. The symptoms disappeared after subtotal thyroidectomy, but manifested themselves again one and one-half years later, when the basal metabolism reached plus 64. The cervix was normal, there were no accessory nor aberrant glands; nevertheless a tumor was discovered in the ovary, the histologic examination of which indicated: struma with marked hyperplasia of the epithelium.

The tumor was removed, and a month later the basal metabolism decreased to plus 8, the signs of hyperthyroidism vanished completely, which plainly shows the relation that existed between the clinical picture and the ovarian struma.

J. P. GREENHILL.

Rieper, J. P.: Comparative Study of Colposcopy and Histologic Findings in Cervical Lesions, *An. brasil de ginec.* 10: 300-308, 1945.

The author examined twenty women by means of the colposcope and then removed areas of diseased cervical tissue for histologic study. Comparative studies showed that colposcopy permits a correct interpretation of cervical lesions in most instances. In the opinion of the author, biopsy may not correctly explain some cervical lesions. Early carcinoma and atypical epithelial proliferations may readily be recognized by the colposcope, but this instrument is not suitable for advanced cases. Syphilitic and edematous lesions interfere with colposcopic diagnosis. Personal experience with the colposcope is essential for proper utilization of this instrument.

J. P. GREENHILL.

Schoekaert, J. A., and Ferin, J.: Endometrial Biopsy as a Diagnostic Aid in Tuberculosis of the Internal Female Genitalia, *Uit de Verhandelingen van de Koninklijke Vlaamse Academie Voor Geneeskunde Van België* 4: 5, 1942.

Thanks to the systematic use of endometrial biopsies in gynecologic cases, the authors have been able to discover tuberculosis of the endometrium in more than 2 per cent of their

Sáez, Eduardo Valenzuela: Concerning the Physiopathology of the Cervix and a Modality of Complete Dilatation in Certain Cases of Dystocia of the Lower Pole of the Ovum, *Obst. y ginec. latino-am.* 4: 280-288, 1946.

The author believes that the character of cervical dilatation is a better criterion for the differentiation between the normal and pathologic courses of labor than are uterine contractions. He reviews the different factors involved in the process of normal delivery, and emphasizes the importance of correct preparation of the birth canal before labor begins. He studied the uterine contractions, the intraovular tension, the cervical musculature, the loosening of the lower pole of the ovum, the bag of waters, and the engagement of the presenting part. He insists upon a peculiar modality in certain cases of dystocia of the lower pole of the ovum when the bag of waters is not properly ballooned out by the engagement of the presenting part. In such cases the dilatation of the cervix is complete, but the cervix has the appearance of a postpartum cervix in that it is totally relaxed. The author believes that the condition is due to lack of engagement and is not inherent in the cervix. Therefore, he believes that the baby should be extracted in such cases. This opinion is borne out by the fact that very few of the babies were born spontaneously.

J. P. GREENHILL.

Perez, Manuel Luis, and Baldí, Eduardo M.: The Risks of the Induction of Labor by Aburel's Method, *Obst. y ginec. latino-am.* 4: 8-19, 1946.

The method of inducing labor adopted by Aburel, namely intra-ovular injection of serum, is popular in South America. The authors encountered three accidents in a series of twenty-five cases. In the first case, the baby showed marks of the needle puncture after delivery; in the second case, the mother died as the result of necrosis of the uterine wall followed by peritonitis, and in the third case the baby developed necrosis of the right leg which resulted in its death.

The authors warn general practitioners against using the Aburel method because, in spite of the advantages of the transabdominal method of inducing labor, a drug which will be harmless for the mother and baby has not yet been discovered.

J. P. GREENHILL.

Gosende, Julio C.: Breech Presentation, *Bol. Soc. de obst. y ginec.* 24: 540-545, 1945.

At the Rosario Maternity Hospital in Buenos Aires from 1930 to 1944, there were 15,298 deliveries. Among them were 386 breech deliveries, an incidence of 4.35 per cent. The total fetal mortality was 21.42 per cent, of which 14.8 per cent were in primiparas, and 6.42 per cent in multiparas. The author emphasizes that breech presentation should be considered under the head of dystocia and not normal labor. In most cases x-ray studies should be made during pregnancy and also during labor. Cesarean section is rarely selected for breech presentation alone, however, when there are additional factors such as contracted pelvis, placenta previa, and advanced age, cesarean section is indicated.

J. P. GREENHILL.

## Menopause

Barber, H. W.: Dermatoses of the Menopause, *Practitioner* 156: 333, 1946.

A considerable number and variety of cutaneous changes and of symptoms referable to the skin appear in women near, during, and/or following the menopause, and at an earlier age in those with ovarian hypofunction. Moreover, certain dermatoses, which may occur from childhood to old age, in either sex, may be markedly influenced in their distribution and clinical manifestations, by the menopause. A good deal is known about the pathology of the menopausal and postmenopausal states, but there remains much unknown, particularly regarding the dermatoses. A great deal is known clinically; less, perhaps, therapeutically. However it is a well-established fact that by the judicious use of estrogens many symptoms referable to the skin and associate nervous system are successfully managed. It should be thoroughly understood, however, that estrogen therapy is not a panacea for "all and every"

If the mortality caused by myomectomy varies between 1.5 per cent and 3.6 per cent, according to the majority of statistics, the one corresponding to the myometrectomy, according to the author's own statistics, which is the most important one up to the present day, is only 1.4 per cent.

J. P. GREENHILL.

Ahumada, Juan C., and Chevalier, Raúl M.: Tubal Surgery and Sterility, *Obst. y ginec. latino-am.* 4: 71-96, 1946.

The authors review the extensive literature dealing with plastic operations on the Fallopian tubes and implantation of the ovary on the uterine cornu for the purpose of overcoming sterility. They explain in detail and illustrate most of the operations known as salpingostomy, salpingolysis, implantation of the tube, and the Estes operation. They present the indications, the postoperative sequels, the percentages of success as reported in the literature, as well as their own experiences.

The authors have performed 12 surgical interventions. Tubal patency tests were performed on 8 patients and the tubes found open in five cases. Two patients became pregnant; one had an abortion, and one had a normal labor and live baby.

J. P. GREENHILL.

### Labor, Management, Complications

Monatno, A.: Labor and Sudden Death, *Obst. y ginec. latino-am.* 3: 945-952, 1945.

There are many conditions that are able to produce sudden death during labor, the most frequent of which possibly is occlusion of the pulmonary artery through emboli or thrombosis. When the clot is large enough to entirely obstruct the artery, the circulation through the whole organism is interrupted, and death occurs nearly instantaneously, without permitting any affection to develop in the lungs. When, on the contrary, the clot is small and only obstructs one of the branches of the artery that supplies a lobule, and especially with stagnation of the blood in the veins (i.e., chronic congestion through heart failure, etc.), an infarct, generally of the hemorrhagic type, appears. This usually does not provoke important disturbances for the patient and disappears in about eight days. Its clinical diagnosis, with the help of some laboratory tests, is as a rule simple, and the most frequent complications are infection of the infarct, repetition, and emboli, which are nearly always fatal.

Treatment of massive emboli is practically impossible. With regard to branch emboli, the indications are: complete rest, oxygen, injections of morphine and papaverine, evacuating enemas, etc. Prophylaxis consists in facilitating the blood flow (by teaching the patient to breathe before and after childbirth), in order to ensure proper ventilation of the lungs.

The most important measure is to avoid infarcts. This consists in modifying the process of blood clotting through the combined use of heparin and dicoumarol, until a prothrombin time of 25 to 30 seconds is attained. Unfortunately, this therapy is not within the possibilities of the general practitioner.

J. P. GREENHILL.

Bass, S.: Experiences With Ergobasin Preparations for the Induction of Labor and in the First Stage of Labor, *Gynaecologia* 121: 3-28, 1946.

This is a report of a method of stimulating labor pains by repeated administration of small doses of quinine, Basergin, and Thymophysin. Special attention is devoted to the effect of Ergobasin. In primary uterine inertia the effect on the whole is good. Great differences occur in the induction of labor according to the indication. In cases of premature rupture of the membranes, the method is practically 100 per cent successful, and in case of prolonged pregnancy failures occur in about one-third. In comparison with the normal, the number of complications in the 437 deliveries was not increased. Ergobasin is harmless if given with care.

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ovarian hormone that has an androgenic action, or for a modified secretion that disturbs the balance between the hormones acting during the menstrual cycle. The histologic characteristics of some theca-cell tumors of the ovary closely resemble the theca-cell proliferations in atretic follicles.

HARVEY B. MATTHEWS.

Gori, Roberto M., Bettinotti, Alberto E., and Bayona, Ernesto: Considerations Concerning the Reactions of Soskin, Wachtel, and Hechter, *Obst. y ginec. latino-am.* 4: 190-208, 1946.

Modern investigations have shown that the process of menstruation is controlled by the vessels of the endometrium, the changes in which are apparently due to the action of acetylcholine. Therefore, delayed menstruation is now considered to be the result of transient hormonal dysfunction, and in many cases is due to mental, emotional, and other factors. Soskin, Wachtel, and Hechter recommended that these patients be treated with prostigmine, the action of which is similar to that of acetylcholine but without its unpleasant secondary reactions. Prostigmine may also be used for the diagnosis of pregnancy. The authors used prostigmine in 150 women who complained of delayed menstruation. The authors believe that this substance may be safely used to produce bleeding when the delayed menstruation is not due to pregnancy. When bleeding occurs, pregnancy may be ruled out. When bleeding does not occur, further studies must be made.

J. P. GREENHILL.

Blanchard, Oscar: Vaginal Smears in the Diagnosis of Ovarian Activity in Women, *Obst. y ginec. latino-am.* 4: 107-132, 1946.

The author reviews the literature on the subject of cyclic variations in the vaginal mucosa. He points out that the normal vaginal cycle exhibits five principal phases: (1) menstruation, (2) proliferative or follicular phase, (3) intermenstrual period, (4) regressive or secretory phase and (5) premenstrual period. In his study the author used Shorr's method.

In a series of 130 patients, 68 were studied completely for menstrual disturbances. The vaginal smears were taken every other day for a minimal period of forty-five days. In some patients the smears were continued for nearly two years. The author found that vaginal smears proved to be of great help in clarifying menstrual disturbances as well as giving clues to therapeutic action by means of hormones such as estrogens, progesterone, androgens, gonadotrophins, etc.

The author concludes that vaginal smears, like most laboratory studies, are useful diagnostic aids if utilized during complete cycles long enough to eliminate sources of error in their reading and interpretation. However, the vaginal smears must be correlated with or subordinated to the patient's history and the physical examination of the woman.

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menopause symptom, for it is a fact that many women do not exhibit strictly menopausal symptoms—and therefore do not need hormone treatment simply because they are passing through or have passed the climacteric, often many years previously.

In conclusion, the author emphasizes that just because a patient is approaching or actually in the midst of the menopause, organotherapy is not necessarily indicated; that the most reliable method of administration is implantation under the skin of estradiol of one of the synthetic estrogens. This method is contraindicated, however, if the patient is still menstruating or has only recently ceased; that hypodermic administration is indicated where rapid and intensified effect is desired; and that oral administration is less satisfactory because of the fact that it is always questionable just how much absorption of the active principle is obtained through this route. Ointments containing a high concentration of synthetic estrogens are now available and, for certain of the dermatoses, this form of therapy may be adequate.

HARVEY B. MATTHEWS.

### Menstruation, Dysmenorrhea, etc.

Culiner, A.: The Relation of Theca-Cells to Disturbances of the Menstrual Cycle, *J. Obst. & Gynaec. Brit. Emp.* 52: 545, 1945.

In a previous study it was shown that the baboon, when the theca cells surrounding the ovarian follicles proliferate or luteinize so extensively as to be visible to the naked eye as yellowish plaques or masses, there is often disturbance of the menstrual cycle. There has been much speculation as the endocrine function of the theca cells, especially in relation to theca-cell tumors. The author has made a study of the ovaries and uteri obtained at operation on women with excessive bleeding or other uterine evidence of endocrine disorder. Many of these patients were in the fourth and fifth decades of life, and had previously had normal cycles and pregnancies. Serial sections of the ovaries were examined.

As the ovaries are removed as a rule only for some gynecologic complaint, it is difficult to establish the incidence of theca lutein cells other than those related to corpora lutea in the normal human ovary. In the author's series, luteinized theca-cells were found more frequently than was anticipated, but their extent and distribution was not closely related to the severity of the menstrual disorder. The author proposes the following classification of theca-cell proliferations on the basis of their relation to various types of atresia. Group I, corpus thecale luteum, in which the original form of the follicle is retained; in one subgroup (a) granulosa cells may be absent or degenerating; in another subgroup (b) granulosa cells are luteinized. Group II, corpus thecale luteum fibrosum, in which granulosa cells are not present, absorption of liquor folliculi has taken place, connective tissue cells fill the cavity and may be surrounded by a hyaline ring; luteinized theca cells are external to this ring. Group III, corpus thecale luteum candicans, in which lutein reactions occur around a collapsed corpus atreticum. Group IV, corpus thecale luteum hyalinum, in which there is a lutein reaction around follicles that have collapse with hyaline tissue invading the cavity. Group V, corpus thecale luteum restiforme, in which a lutein reaction occurs around primordial or small maturing follicles. All these types of theca-cell proliferation with luteinization have been observed in the author's material except Group V, which, however, is theoretically possible. In this material a wide range of endometrial reactions and clinical disturbances was observed, but those could not be correlated with the type of theca-cell luteinization observed in the ovary. In a few cases, normal endometria were found, although luteinized theca-cells were present in the ovaries, and there were menstrual disturbances.

From these observations, the author concludes that theca-cell proliferation may occur as part of the process of maturation of the Graafian follicle. Luteinization of theca-cells around atretic follicles may be without clinical significance in ovulatory cycles, but in the presence of extensive thecal luteinization with follicular atresia, disturbances of menstrual rhythm and abnormal bleeding may occur. From the character of the uterine reactions found in association with proliferation of theca-cells, neither estrogenic nor progesteronic action can be definitely attributed to them. It is possible that they are responsible for a third

## Items

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### **The Third American Congress on Obstetrics and Gynecology**

The Third American Congress on Obstetrics and Gynecology will be held from September 8 to 12, 1947, in the Municipal Auditorium in St. Louis, Missouri. Dr. Fred L. Adair of Chicago is the General Chairman.

While the Third Congress is similar in scope and program to the two previous meetings, it will be larger in every way. The program under the direction of Dr. William F. Mengert of Dallas is being made up to appeal to the obstetric and gynecologic specialist, to the general practitioner interested in those fields, to the hospital administrator, and to nurses. The program will include sections for the public health doctor and the public health nurse. The medical section of the program is under the direction of Dr. Ralph A. Reis of Chicago as in 1942.

The scientific exhibits are under the guidance of Dr. Jean Paul Pratt of Henry Ford Hospital. The moving picture program is being made up by Dr. John Park of Washington, D. C. Dr. John Rock of Boston heads the committee on evening speakers. The technical exhibit has been arranged by Dr. Philip F. Williams of Philadelphia. A membership committee in every state and in the territories is being set up by Dr. Ralph E. Campbell of Madison, Wisconsin, and plans are under way to have a special committee build up interest in the Congress in Central and South America. Dr. Harvey B. Matthews of Brooklyn heads the committee in charge of publicity. The general advisory committee is in charge of Dr. Howard C. Taylor, Jr. The local organization committee in St. Louis is headed by Dr. Richard Paddock.

The Friday morning sessions of the Congress, September 12, are to be given over entirely to the National Federation of Obstetric-Gynecologic Societies. The program for these sessions will be arranged by a committee working under Dr. James S. Taylor of Altoona. One member of this committee, Dr. E. Lee Dorsett of St. Louis, will arrange an evening speaker for the Federation of nation-wide prominence who will present his viewpoints to a joint meeting of the Congress, the Federation, and the general public. For further information, address Karl S. Richardson, 24 West Ohio Street, Chicago, Ill.

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### **International Congress of Obstetrics and Gynecology**

**Dublin, Ireland, July 7 to 12, 1947**

The program for the Congress includes seven sessions to be devoted on successive days to the following topics: history of midwifery, puerperal sepsis, eclampsia, sterility, fetal and neonatal mortality, and shock in obstetrics. Representative speakers from several countries will discuss these topics, including the British Isles, New Zealand, the United States, Australia, South Africa, Sweden, Palestine, Denmark, Canada, and elsewhere.

Information about travel routes, hotel accommodations, etc., may be obtained from the local offices of Messrs. Thos. Cook and Sons.

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### **American Association of Obstetricians, Gynecologists, and Abdominal Surgeons' Foundation Prize**

An annual contest for this award is open to all physicians. Further information may be obtained from the Secretary of the Association, Dr. James R. Bloss, 418 Eleventh Street, Huntington 1, West Virginia.



## Correspondence

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### Vaginal Lacerations Resulting From Coitus

*To the Editor:*

Since writing a report of three cases of vaginal lacerations resulting from coitus, published in the January issue of the JOURNAL (53: 177, 1947), I have encountered another similar case, of special interest because of the patient's age.

CASE 4.—Mrs. M. K., aged 72 years, white, was brought to the hospital at 7:30 P.M. on Nov. 16, 1946, because of profuse vaginal bleeding of two and one-half hours' duration. Her granddaughter stated that the blood had saturated two Turkish towels. The patient offered no information as to the cause of the bleeding. She was faint, her skin was moist and clammy, although her blood pressure was 120/70, her pulse was 80, and of good volume. On pelvic examination, the vulvar and vaginal tissues were found to be elastic and in a good state of preservation for the patient's age, and the introitus admitted two fingers easily. The uterus and adnexa could not be felt. Vaginal bleeding was still profuse, but the cervix remained dry when exposed and sponged. To the right of the cervix, extending through the thickness of the vaginal mucosa, was a fresh laceration, about 3 cm. in length, which was still bleeding. The patient was taken to the operating room, anesthetized with sodium pentothal, and the laceration was repaired. Upon further questioning about the cause of the injury, the patient finally admitted having had voluntary intercourse. Coitus had been painful, and was followed immediately by vaginal bleeding.

The patient is the mother of two children, aged 54 and 53 years. She had a spontaneous menopause thirty years ago, at the age of 42 years, and had not had sexual intercourse for the past sixteen years.

No mention is made of coital trauma as a cause of postmenopausal bleeding in what are perhaps the two most widely quoted papers on the latter subject (Taylor, H. C., Jr., and Millen, R., "The Causes of Vaginal Bleeding and the Histology of the Endometrium After the Menopause," *AM. J. OBST. & GYNEC.* 36: 22-39, 1938, a study of 406 cases of postmenopausal bleeding at Roosevelt Hospital between 1921 and 1935; and TeLinde, R. W., "Causes of Postmenopausal Bleeding," *Am. J. Surg.* 48: 289-293, 1940, a review of all the cases of postmenopausal bleeding seen in the Johns Hopkins Hospital between 1918 and 1935).

HAROLD SPEERT, M.D.

THE ROOSEVELT HOSPITAL  
NEW YORK CITY  
Nov. 22, 1946.

fibrous tissue. This was true especially in the portio vaginalis where only a few muscle fibers were found; the supravaginal cervix was reported to be mainly smooth muscle. Novak<sup>4</sup> is in general agreement with these findings. Stander,<sup>5</sup> on the basis of this work and his own studies, considers the cervix as mainly fibrous. During pregnancy, Stieve found that the muscle tissue (presumably that of the portio supravaginalis) regressed from the second month onward; by late pregnancy there were fewer muscle fibers than in the nonpregnant state. Werth and Grusdew are quoted as finding the cervix in late pregnancy uncommonly poor in muscle, and R. Schmidt as emphasizing that at the end of pregnancy the lower third of the cervix is practically always pure connective tissue. In the monkey, an abundance of "fuchsinophile" tissue is found in the cervical colliculi.<sup>6</sup> With these exceptions, most present-day discussions of the anatomy of the uterus consider the cervix as being a muscular structure, and infer that its fibrous tissue content is of incidental interest.

II. *The Isthmus Uteri*.—Our present understanding of the isthmus uteri is based upon the work of Aschoff,<sup>7</sup> who first defined the structure in 1905, and in later articles<sup>8-10</sup> outlined its changes during pregnancy. His observations were confirmed and extended by Stieve.<sup>3</sup> The work of these two men served to crystallize the previous conflicting opinions into a concept which is handed down to us today virtually intact. It is the purpose of this brief review to present the classical concept of the isthmus as it was originally outlined and as we understand it today. Later, exception will be taken to certain of its tenets.

In the nonpregnant uterus, Aschoff recognized two internal uterine ora: the histologic internal os which marked the microscopic point of transition from endocervical mucosa to isthmus mucosa, and the anatomic internal os some 6 to 10 mm. superior to this. The latter is defined as a constriction in the uterine lumen, marking the lower boundary of the corpus uteri. The structure lying between the planes of these two ora was designated as the isthmus uteri. By definition, by the Nomenclature Commission of the British Anatomical Society, and by B.K. Nomenclature, it is an entity in itself, separate and distinct from cervix and corpus. Its physiologic behavior is described as being unique. Its mucous membrane was found to be generally characteristic of corporeal endometrium, though thinner, and richer in supporting tissue. Its glands are more sparse than the glands of the corpus, less sensitive in their response to the ovarian hormones, and are said to be glycogen-free.<sup>11</sup> With regard to the boundaries of the isthmus, there is general agreement that both anatomic and histologic ora are commonly inconstant, thus imparting at the very outset a somewhat nebulous quality to this structure. First, the histologic internal os is often found to be indefinite, cervical, and isthmus glands being intermingled over a sufficient distance that the transition point cannot be definitely delineated. Second, the character of the constriction itself is not constant. If the constriction were knifelike, it could be marked precisely. But most frequently it is merely a rounded eminence in the uterine lumen. In some cases the constricted area is quite long, and the isthmus is said to be contained within the confines of this narrowed area. Aschoff's original drawing will illustrate the latter instance (Fig. 1). Despite these inconstancies, several observers have attempted to measure the length of the isthmus. Stieve gives the length of the isthmus in a nonpregnant uterus as 4.5 mm.; Aschoff considers the normal range as 6 to 10 mm.; Kearns,<sup>12</sup> 5 mm.; Marshall,<sup>13</sup> 5 to 10 mm.; Fränkl<sup>11</sup> merely concludes that the length of the isthmus is "extraordinarily variable."

The classical concept of the isthmus changes during pregnancy may be summarized as follows: During the third month of pregnancy the isthmus elongates to approximately three times its former length; this is said to be accompanied by proportionate thinning of this segment, since no significant change in mass is noted at the time of the elongation. During the subsequent weeks

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## Original Communications

### THE FIBROUS NATURE OF THE HUMAN CERVIX, AND ITS RELATION TO THE ISTHMIC SEGMENT IN GRAVID AND NONGRAVID UTERI\*

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IN THE course of routine study of anatomic and gynecologic specimens it was noted that the human cervix is composed predominantly of fibrous connective tissue rather than smooth muscle. The fundamental tissue of the uterine wall superior to the cervix was composed of smooth muscle which did not differ significantly from that of the corpus. Though the literature contains several references to this structural difference between cervix and corpus, the findings were admittedly a source of much amazement to the present writer. They led to an inquiry into the validity of our present concept of the isthmus uteri and its purported changes during pregnancy. Accordingly, the cervix and isthmic segment were studied in 12 pregnant and 46 nonpregnant uteri. The findings suggest certain fallacies in our present understanding of the anatomy and physiologic significance of the isthmus. Also, they provide an explanation for certain of the cervical and isthmic phenomena of pregnancy which have not been fully understood.

#### Previous Concepts

I. *Cervical Structure.*—The techniques which have been used in the study of cervical structure include gross dissection and the examination of tissues stained either by routine methods or by contrast stains. By one or the other of these means, Hofmeier,<sup>1</sup> Aeconci,<sup>2</sup> and others imply that the cervix is fundamentally fibrous. Later work led to the conclusion that the cervix is a muscular structure, a thesis to which most present-day workers adhere. Among modern writers, only a few regard the cervix as fibrous. Stieve's examination of a normal nonpregnant uterus<sup>3</sup> revealed the cervix to be abundantly supplied with

\*Presented at a meeting of the Chicago Gynecological Society, Oct. 18, 1946.

*Fixation of Tissues.*—Bouin's fixation was employed for all of the pregnant and most of the nonpregnant uteri; for the remainder, Zenker's was used. Bouin's is preferred principally because of the great rapidity with which it penetrates the tissues, and also because of the extreme clarity of the final preparations.

*Nonpregnant Uteri.*—All of the material was selected at random with the requirement only that the cervix and isthmic segment be not distorted by tumor growth. Thirty-two specimens were prepared by Dr. E. L. Benjamin of Northwestern University. In these, an attempt was made to correlate a gross, fixed landmark in the uterine cavity with the level of the change from endocervical to isthmic mucosa. The smallest Hegar dilator which met with obstruction was passed to the level at which such obstruction occurred. The distance of penetration was noted, the uterus sectioned transversely one centimeter superior to this level, and the level itself marked by means of a transverse incision which extended two-thirds of the distance through the uterine wall. Blocks of the entire cervix and isthmic segment were then prepared for microscopic examination.

In fourteen uteri, in which similar blocks were prepared, the level of the histologic internal os was examined with reference to the fibromuscular junction (v.i.), and a correlation of these two levels made.

*Pregnant Uteri.*—The data deemed pertinent to this paper are noted in Table I.

TABLE I

SPECIMEN NUMBER	MENSTRUAL AGE (WEEKS)	AGE DETERMINED BY CROWN-RUMP LENGTH OF FETUS (WEEKS)	PATIENT'S GRAVIDITY	PATIENT'S PARITY
A-1	17½	—	9	3
A-3	17	—	5	3
1	8	5	1	0
4	8	8	4	3
5	14	12	10	7
6	22½	19	8	3
7	14	13 (Twins)	2	1
8	15½	17	5	4
9	—	12½	—	—
10	—	12	9	5
11	10½	10½	4	3
12	—	14	—	—

The specimens were all removed for reasons other than local uterine disease. They are considered as normal, except for the occasional incidental finding of small fibroids in the body of the uterus.

In the pregnant specimens it was desired to retain the original shape for purposes of later illustration. For this reason the entire specimen was immersed in Bouin's solution for thirty minutes to an hour prior to sectioning. At the same time, Bouin's solution was injected into the tissues of the sagittal plane throughout the circumference of the uterus, by means of a syringe and small needle. After the external aspects were fixed sufficiently to allow opening without collapse of the organ, a frontal section was prepared. The location of the placenta was determined, and the membranes were gently stripped away from the opposite uterine wall. The two halves were then placed in Bouin's solution until completely fixed. Thereafter they were removed to 70 per cent alcohol, measured, and drawings were prepared. A strip 5 mm. thick was cut from the sagittal plane for microscopic sections. Blocks of appropriate size were then cut and dehydrated according to the usual procedure for this fixative.

"unfolding" occurs, such that the entire isthmic canal is incorporated into the formation of the ovum chamber. At this time the uterine cavity consists of cavum corporis plus the widened isthmic canal. The isthmus is now referred to as the "lower uterine segment," and remains as such until the uterus returns to its nonpregnant state. The unfolding was noted to stop within a few millimeters of the histologic internal os. Stieve believed that the musculature played no part in thus limiting these changes, and makes no reference to the fibrous content of the cervix nor to a transition from one type of tissue to another. However, he describes a system of blood vessels at the junction of cervix with isthmus, of sufficient complexity to be referred to as "erectile tissue." To this he ascribes the functions of delimiting unfolding of the isthmus, and of maintaining closure of the uterus until the onset of labor.

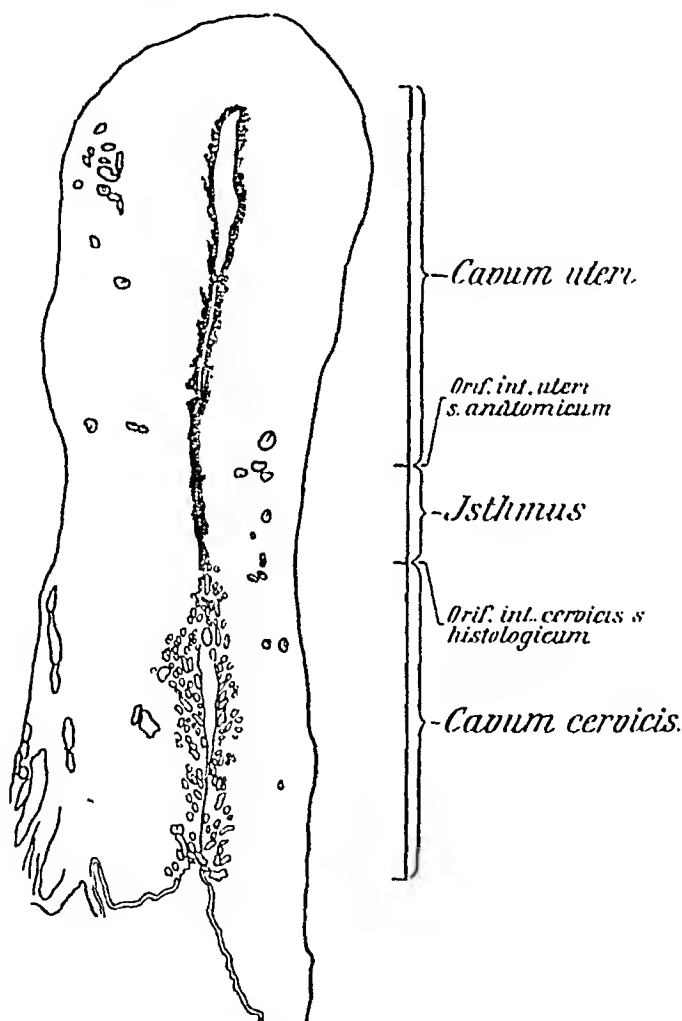


Fig. 1.—See text. (Reproduction from Aschoff, L.: Zeitschrift für Geburtshilfe und Gynäkologie 58: 328, 1906.)

### Materials and Methods

The original material consisted of 12 pregnant uteri and 46 nonpregnant uteri. Fifteen additional nonpregnant cervixes have been sectioned with results which are in accord with those to be presented. All of the specimens were of human material which was removed surgically. They were obtained directly from the operating table and removed immediately to the laboratory where they were sectioned and fixed.

able. Sometimes it is abrupt and immediately complete, while in others it may be extremely gradual, occurring almost imperceptibly over the course of 5 or (at most) 10 mm. In some instances the plane of the transition is straight across the uterine wall; but more often the line is a wavy one. It is of interest that not only may the nature of the transition line vary in different portions of the same cervix, but also its level with respect to the external os may vary as much as 6 or 8 mm. In these specimens there was no definite correlation of the patient's age, parity, and the local cervical lesion with the nature of the fibromuscular junction. In general, the transition was less gradual in the more normal specimens. Five uteri were obtained from nulliparous women of child-bearing age. The cervices were quite normal, the fundamental tissue was fibrous, the smooth muscle was sparse and widely scattered, and the fibromuscular junction abrupt.

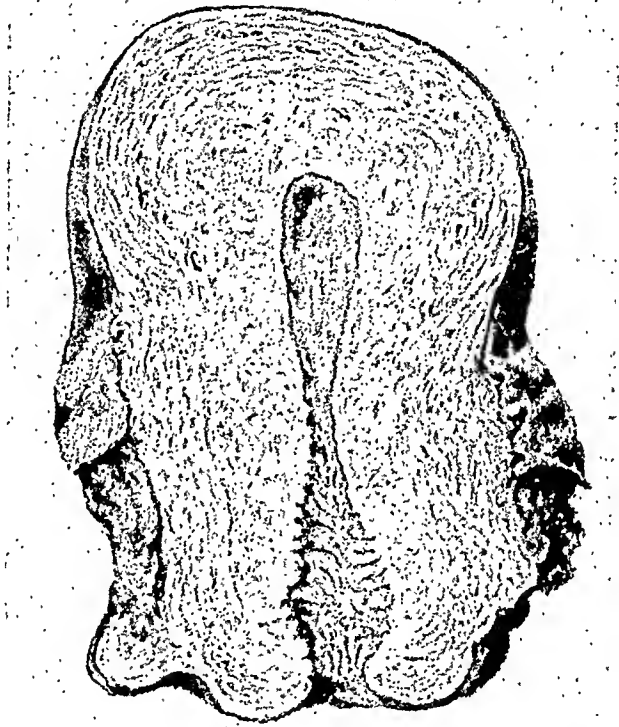


Fig. 2.—Frontal section of a normal human uterus. The constriction in the uterine cavity is gradual. The precise level of the anatomic internal os is indefinite. (X1.)

B. *Correlation of the level of the histologic internal os (H.I.O.) with a fixed point in the isthmus—an attempt to measure the length of the isthmus:* It should be mentioned here that there are two possible means of distinguishing Aschoff's anatomic internal os (A.I.O.). First is by examination with the naked eye. The inadequacy of this judgment is illustrated both by Aschoff's original section (Fig. 1) and by Fig. 2, a frontal section of an essentially normal uterus. In the latter, one might conscientiously place the A.I.O. at any point over the course of 4 millimeters. Though small, this distance is considerable when dealing with a structure whose purported length is less than 1 cm., and is even estimated by some to the fraction of a millimeter. Second is the use of a Hegar dilator after the manner indicated above. This method is admittedly indefinite, for three major reasons: (1) the rounded tip of the instrument does not allow precise measurement of the lower end of the constriction; (2) the lower end of the constricted area may be variously related to the true A.I.O., for the isthmie canal may be either straight or divergent; (3) fixation subse-

*Stains.*—Histologic details were demonstrated by routine *hematoxylin and eosin stains*. *Mucicarmine* stains were employed principally to distinguish the level of the histological internal os. This is ordinarily not needed, but it is useful in occasional instances. Cervical mucus, endocervical mucosa, and the cells lining the cervical glands take a deep red stain, while all other tissues containing no mucus show only the brown counterstain. Masson's trichrome (iron-hematoxylin-acid fuchsin-aniline blue) method was employed to distinguish smooth muscle from fibrous tissue. Smooth muscle fibers and nuclei are stained pink or red, fibrous tissue a vivid blue. This stain is considered as specific, and when carefully done using tissues that are properly prepared, its results are believed to be diagnostic. Twenty-three nonpregnant uteri from the collection of Dr. George H. Gardner of Northwestern University were studied. These were stained by Milligan's trichrome method,<sup>14</sup> which is similar to that of Masson's aniline blue trichrome except that the method is less exacting, and the fibrous tissue is stained a brilliant green; its results agree with those obtained by the Masson technique. Elastic tissue fibers were distinguished by the *Orcein-Metanil Yellow* technique or by the *Elastin-H* method. Here the elastic fibers are stained brown-black or gray-black in contrast to the remaining tissues which take an amber or violet counterstain.

## Results

### I. The Nonpregnant Uterus.—

*A. Intrinsic structure of cervix and isthmic segment:* The appearance of the cervical wall in routine hematoxylin and eosin stains is familiar. It is composed of interlacing strands of fibrillar tissue which take a light pink stain, show no tendency to strata formation, and, except for the edema which accompanies many cervical lesions, show no significant differences from the uterine wall above the cervix. In some areas the tissue resembles fibrous tissue, in others, smooth muscle. When employing this stain alone, absolute differentiation throughout the entire cervix is considered as impossible.

A very striking picture is obtained by use of differential stains for fibrous tissue and smooth muscle. The basic structure of the cervix is found to be fibrous connective tissue. In many specimens virtually no smooth muscle can be found. From this extreme one passes to other specimens in which moderate amounts of muscle are present; occasionally this may reach as much as 40 or 45 per cent though ordinarily it does not exceed 10 or 15 per cent. When muscle does appear in cervical sections, its distribution shows great variability. Ordinarily the muscle fibers are scattered at random throughout the substance of the cervix. Rarely, they appear in small bundles near the central portion of the tissue, being either isolated or continuous with the muscular tissue superior to the cervix. The inconstancy of such central bundles and their attenuate appearance when they are present make it unlikely that sphincteric possibilities could be attributed to them.

Stains for elastic tissue showed the presence of minute and, to the author's opinion, insignificant amounts of these fibers. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. As one might expect, they were most abundant in and around the walls of the larger blood vessels. Elsewhere they constituted but a fraction of 1 per cent of the total fibrous tissue of the cervix. Superior to the cervix they were also sparse, being for the most part limited to the outer third of the uterine wall and located in the fibrous tissue separating the muscle bundles.

*The fibromuscular junction:* As one ascends the cervix to the region of the histologic internal os, a level is reached where the predominance of fibrous tissue ceases, giving way to smooth muscle. The nature of the transition zone is vari-

elements are not possible with the techniques which have been employed here. There is the distinct impression of the enlargement of both of these elements and of an increase in their number. Also, the presence of edema in the pregnant specimens is quite definite.

By the means which have been used, it is not possible to confirm the reported changes in *elastic tissue* during pregnancy. Elastic fibers are present in the same (negligible) quantity as in the nonpregnant specimens, and with the same haphazard arrangement except with reference to the blood vessels. Elastic stains were available in the corpus in only two of the pregnant specimens. In these the fibers were limited to the outer third of the uterine wall, being interspersed among the fibrous connective tissue which separates the muscle bundles. They were considerably more numerous in the tissue immediately above the cervix.

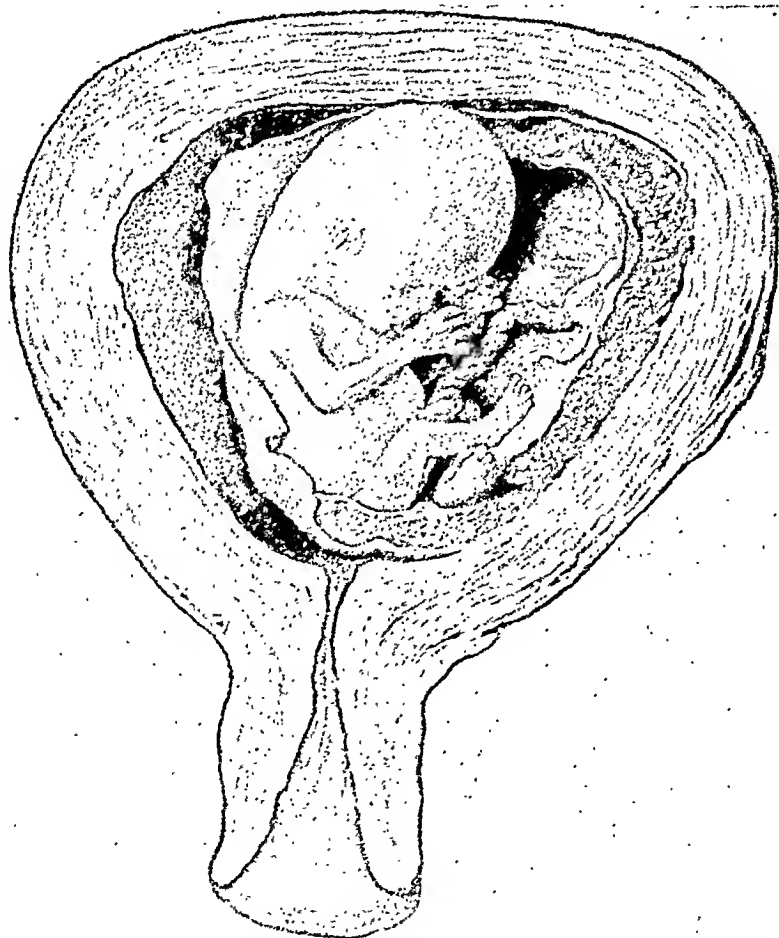


Fig. 4.—Frontal section of uterus No. 10; twelve weeks' pregnancy. ( $\times 5$ .)

With the exceptions of greatly increased vascularity and edema, the fundamental structure of the cervix was found to be similar to that of the nonpregnant specimens. The basic tissue is fibrous. Varying quantities of smooth muscle are present, amounting to from 2 to 40 per cent, with an average of about 10 per cent. The distribution of muscle is likewise variable, though the presence of small bundles in the central portions of the tissue is somewhat more common. When they do appear, the bundles are heavily interspersed with fibrous tissue, and appear to have insignificant sphincteric possibilities.



quent to measurement of the level of the constriction causes distortion which may alter this measurement. Despite these objections, the latter technique was considered preferable, and has yielded information which is significant.

1. In 17 of 32 cases the H.I.O. was sufficiently sharp that it could be delineated precisely, within one millimeter. In 15 of 32 cases the transition from endocervical to isthmie mucosa occurred over a distance which was greater than one millimeter. Of these, the maximum zone of transition was 6.0 mm., the mean was 3.0 millimeter.

2. Employing a mean measurement where the transition was gradual, it was found that in 11 of 32 cases the H.I.O. occurred superior to the point of stoppage of the Hegar dilator (maximum 7.5 mm., mean 3.0 mm.), that is, within the constricted zone. In 21 cases the H.I.O. was located at or below the point of stoppage (maximum 13.0 mm., mean 5.7 mm.).

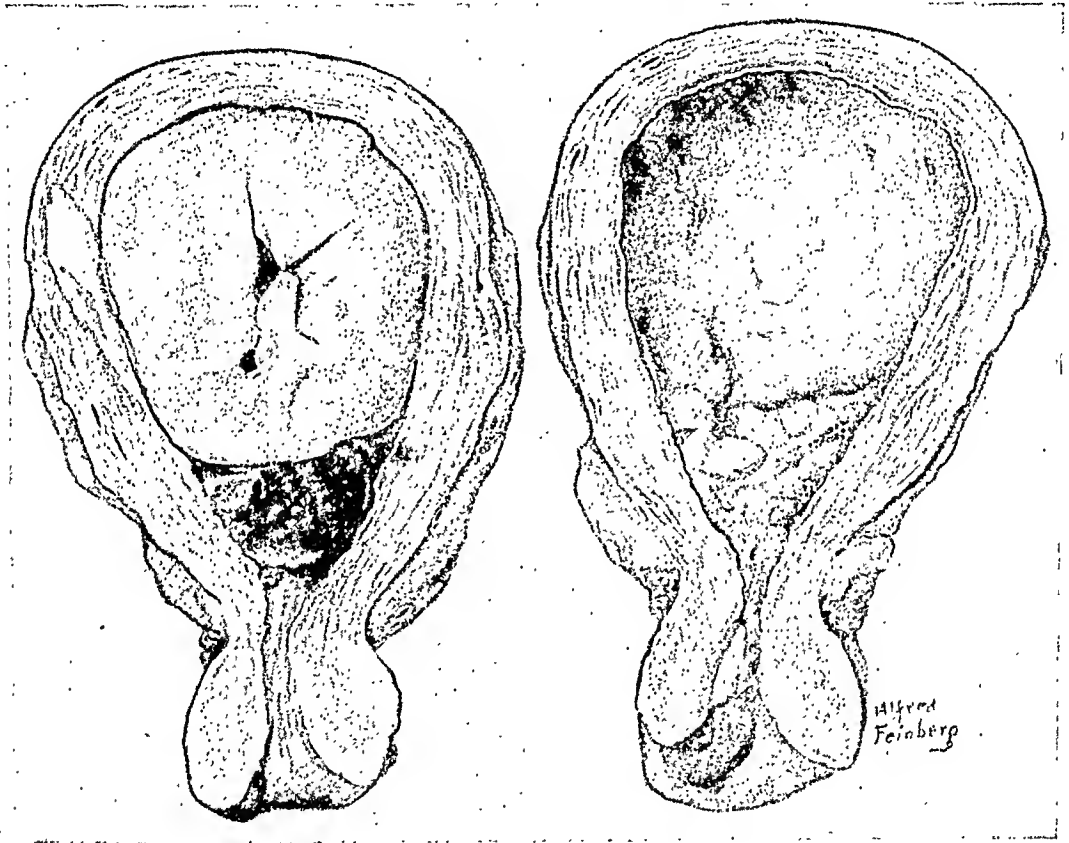


Fig. 3.—Frontal section of uterus No. 4, eight weeks' pregnancy. ( $\times 4\%$ .)

C. *Correlation of histologic internal os (H.I.O.) with level of fibromuscular junction (FM)*: In these cases it was considered pertinent to measure the FM only on the mesial aspect of the cervix, beneath the mucous membrane. The irregular, wavy character of the transition vitiated an accurate correlation elsewhere. In 3 of 14 cases the FM was sufficiently gradual that it could not be definitely placed with reference to the H.I.O. In 8 of 14 cases the H.I.O. was located *below* the FM. In 3 of 14 cases the H.I.O. was located *above* the FM. The average relationship in 11 cases placed the H.I.O. 1.3 mm. below the FM.

## II. The Pregnant Uterus.—

A. *Intrinsic structure of cervix and isthmus during early pregnancy*: Specific estimates of hypertrophy and hyperplasia of the muscle and fibrous tissue

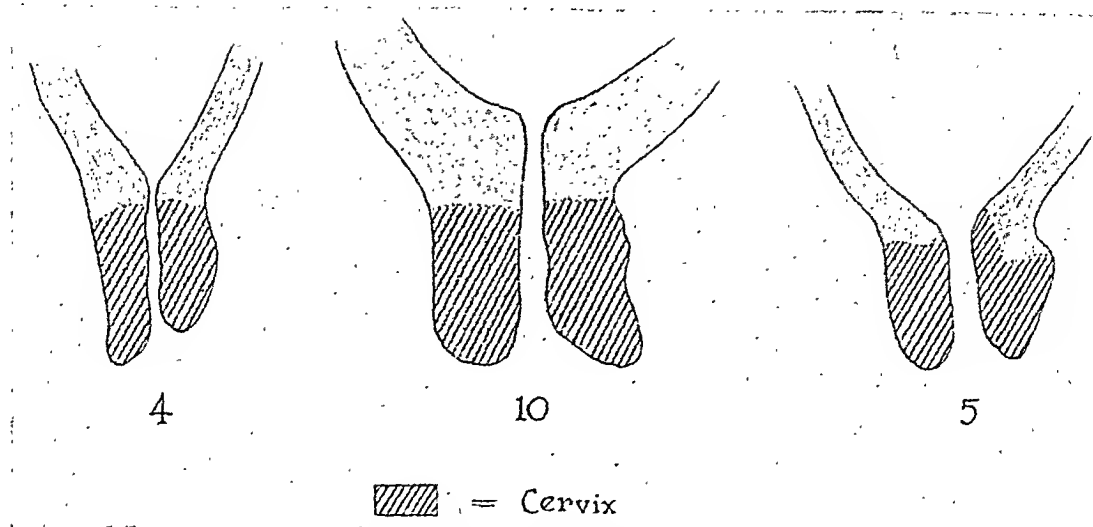


Fig. 6.—Diagram to indicate distribution of fibrous tissue and smooth muscle in the uteri shown in Figs. 3, 4, and 5. The drawings represent tracings of microscopic slides stained by Masson's trichrome, taken from cervix and isthmus segment in the sagittal plane. The crosshatched area represents the portion which is predominantly fibrous, the remainder, that which is predominantly muscular. Note the lengthening of the isthmic canal in uterus No. 10, and the obliteration of this canal in uterus No. 5 after the isthmus is unfolded. In the latter specimen unfolding occurs down to the region of the fibromuscular junction.

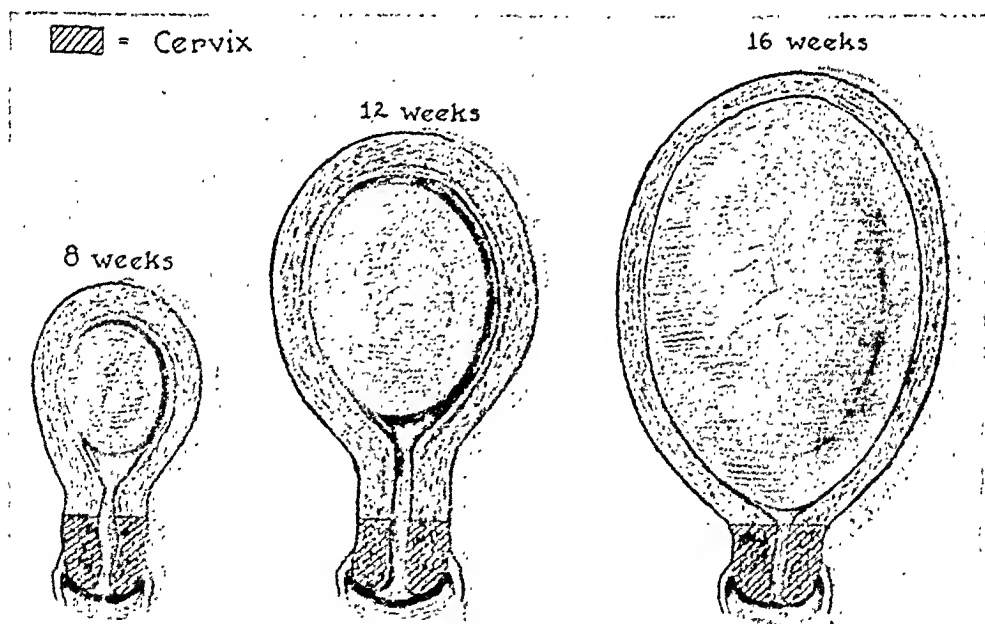


Fig. 7.—Diagram to represent changes in the uterus during early pregnancy. The cross-hatched area represents the portion which is chiefly fibrous, the remainder of the uterine wall being chiefly muscular. At eight weeks the general configuration of the uterus is similar to that prior to pregnancy. At twelve weeks there is hypertrophy throughout the muscularis. In the isthmus segment this is manifest as elongation and slight thickening, which are proportional to the similar changes which occur elsewhere in the muscularis. The products of conception do not yet utilize all of the available space. At sixteen weeks the products of conception have grown sufficiently to require more space than is available superior to the isthmus segment. The isthmus segment has adjusted to these requirements, unfolding to form a part of the wall of the ovum chamber. The unfolding stops inferiorly at the level at which the proportion of fibrous tissue in the uterine wall becomes sufficiently great that such an adaptive relaxation of the muscularis cannot occur.

*B. Changes in the isthmus:* A series made up of specimens numbers 4, 10, and 5 is of interest, since it confirms in part the thesis of Aschoff and Stieve. Uterus No. 4 is that of an eight weeks' pregnancy in a gravida v, para iv. The illustration (Fig. 3) is of a frontal section. The region of the A.I.O. is poorly marked here, but is somewhat more distinct in the sagittal view (see Fig. 6). The products of conception have not yet enlarged sufficiently to fill the rapidly growing uterus. In uterus No. 10, a twelve weeks' specimen from a gravida ix, para v, the distance from the uterine cavity to the external os is greatly lengthened over that of uterus No. 4. This specimen represents the case in which the isthmus is elongated, but has not yet "unfolded." There is no evidence of thinning as an accompaniment to this elongation. The products of conception still do not occupy all of the available space in the uterus. Specimen No. 5 (Fig. 5) is that of a twelve to fourteen weeks' pregnancy from a

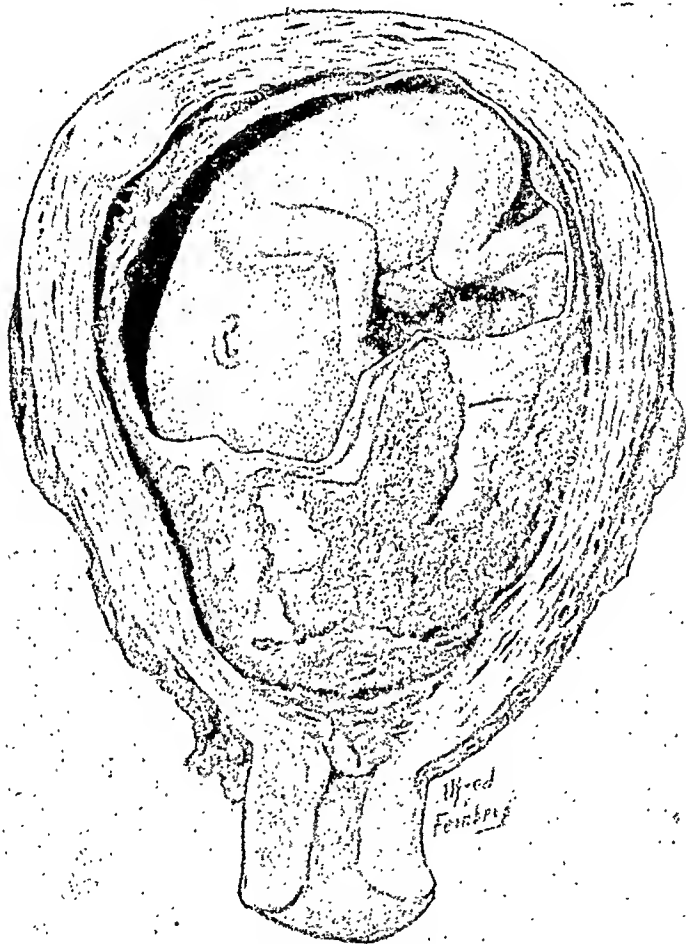


Fig. 5.—Frontal section of uterus No. 5; twelve to fourteen weeks' pregnancy. ( $\times\frac{1}{2}$ .)

gravida x, para vii. The isthmus has unfolded, and the general uterine cavity is now represented by the corpus and the dilated isthmus. The products of conception fill the uterus. The dilated isthmic segment is somewhat thinner.

These phenomena are clarified by the use of contrast stains (Fig. 6). If the extent of the cervix is defined in accordance with the extent of fibrous tissue, one finds, first, that the length of the cervix does not change appreciably during early pregnancy. Second, the elongation which occurs in the isthmus is proportional to that which occurs elsewhere in the muscularis. Third, unfolding,

located *below* the FM. The average relationship in 15 cases placed the H.I.O. within 1 mm. of the FM, the extremes being 5 mm. above, and 6 mm. below.

The findings in regard to over-all measurements, structure of the corpus, changes in the mucous membrane of the cervix, isthmie segment and corpus, alterations in vascularity, and the like, are beyond the scope of this presentation. One might mention in passing the "erectile tissue" reported by Stieve. In five specimens this extreme vascularity was noted near the fibromuscular junction toward the external aspect of the uterus. In the others there was a general increase in vascularity which seemed insufficient to be referred to as "erectile"; nor was it limited to the area in question.

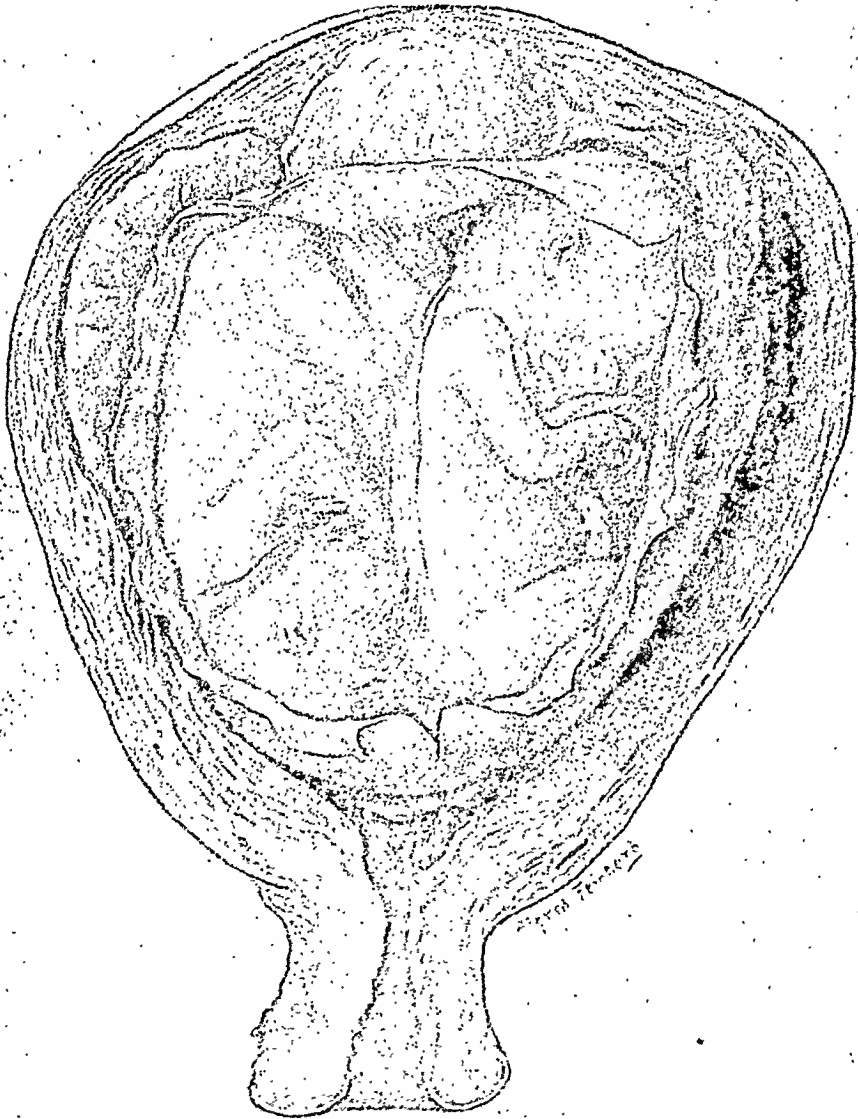


Fig. 9.—Frontal section, uterus No. 7. Twin pregnancy, thirteen to fourteen weeks. ( $\times\frac{3}{4}$ .)

### Discussion

The fibrous nature of the cervix has lesser practical interest in the non-gravid than in the gravid uterus, for it is during pregnancy that this has special significance in the explanation of many of the phenomena which are commonly observed. Most obviously, this observation aids in understanding why the

or dilatation, of the isthmus occurs down to the region of the fibromuscular junction. Further, in these specimens there is the indication that the time of unfolding is related to the question whether the products of conception have grown sufficiently to utilize the space which is available. Though the data are scanty, they suggest that thinning of the isthmic segment occurs after unfolding rather than before. These changes are illustrated diagrammatically in Fig. 7.

In all of the remaining specimens the isthmus is unfolded. The relation of the isthmic musculature to the fibrous cervix is shown in Fig. 8. The corresponding uteri are shown in Figs. 9, 10, and 11. Lack of space prevents inclusion of the remaining specimens; they are in general agreement with those which are shown.

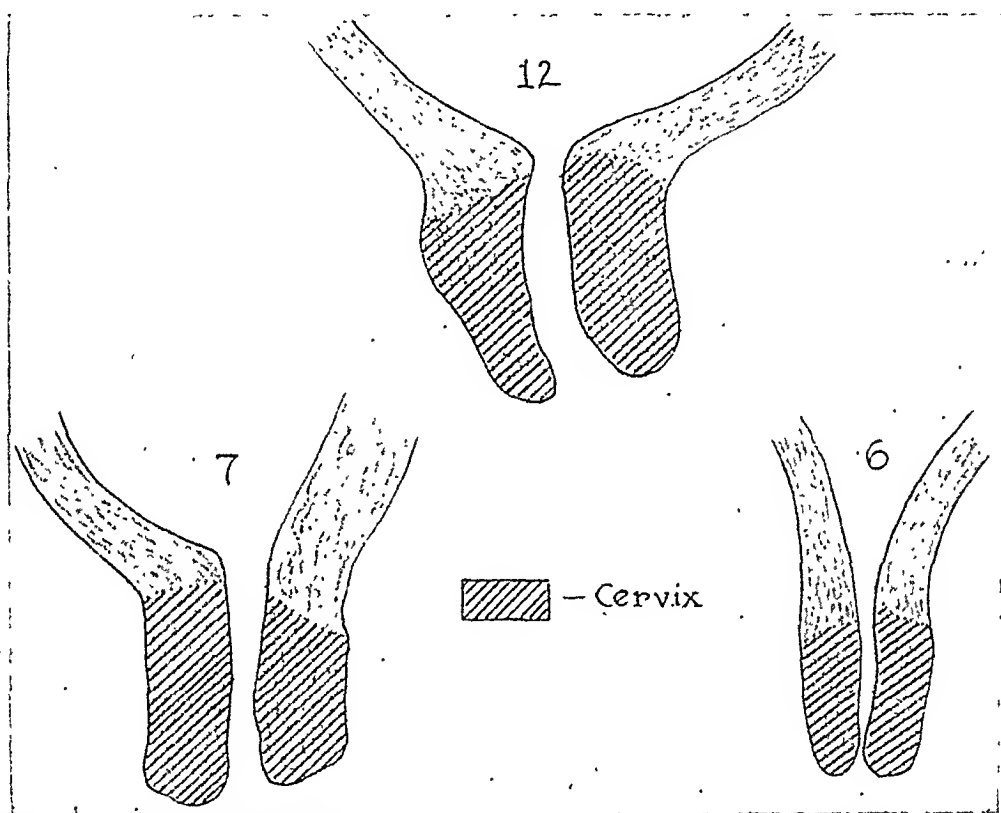


Fig. 8.—Distribution of fibrous tissue and smooth muscle in specimens Nos. 7, 12, and 6. Crosshatched area represents portion which is predominantly fibrous, the remainder, that which is predominantly muscular. Compare with Fig. 6.

In the uteri where the isthmus is unfolded, there is no evidence whatever of the anatomic internal os. The junction of the isthmic segment with the corpus is such that it cannot be distinguished either grossly or microscopically. The firm adhesion of the fetal membranes to the corporeal endometrium and its relatively light adhesion to the isthmic mucosa, as described by Stieve, Aschoff, and others, was not sufficiently marked in our specimens to be of diagnostic use. Also, once the membranes press firmly against the decidua, either corporeal or isthmic, the distinction between the two is nil.

*C. Correlation of level of histologic internal os (H.I.O.) with fibromuscular junction (FM):* This estimation was made in the same manner as in the non-pregnant specimens. Fifteen measurements were made in eight pregnant uteri. In five cases the H.I.O. was located *at* the fibromuscular junction. In seven cases the H.I.O. was located *above* the FM. In three cases the H.I.O. was

boundary of the isthmus (the H.I.O.) is not sharply defined, occurring over an average distance of 3 mm. (2) The upper border of the isthmus (the A.I.O.) cannot be measured accurately, within 1 to 4 mm. For these reasons alone, attempts to measure this segment accurately, and, indeed, to measure it in terms of a fraction of a millimeter, are considered as invalid. (3) The H.I.O. is variable with respect to the constricted isthmic canal, in some cases being as far as 13 mm. below it, in others within it. (4) Superior to the fibromuscular junction, the isthmic segment shows no significant structural differences from the corpus. Because of these observations the question is properly raised as to whether the present definition of the isthmus uteri in the nonpregnant uterus is a valid and necessary designation, or whether it could be sharply modified to advantage. In this connection it is of interest that most current texts of gynecology do not recognize the classical concept of the isthmus which was reviewed above. The major argument in favor of retaining this terminology in the nonpregnant uterus is the peculiar characteristics of the isthmic mucous membrane. But it is questionable whether one has the right, inherent in the present definition, to limit the functional capacity of a muscular structure within the confines of a certain type of mucosa. It is believed, rather, that the isthmic mucosa is best considered as transitional between endocervical mucosa and true endometrium, and that the wall beneath it is better defined in other terms.

The following observations concerning isthmic changes during pregnancy are recorded here: (1) The isthmic segment elongates during the third month of pregnancy, prior to the time when the products of conception have fully utilized the space available in the corpus. This elongation is not accompanied by a mysterious thinning, as though invisible traction were pulling the corpus from the cervix, but rather is accompanied by thickening which seems proportional to that which occurs throughout the corpus. (2) The unfolding of the isthmic segment, with incorporation of its canal into the general uterine cavity, appears to coincide with the time when the ovum fills the cavum corporis, and requires more space to accommodate it. As previously outlined by Aschoff, this process of unfolding is pictured not as active distention but rather as a "passive dilatation," in which the muscularis of the lower pole of the uterus merely adjusts itself to the growing contents of the uterus. (3) The process of unfolding of the isthmus appears to be accompanied by thinning of its musculature. (4) The unfolding stops abruptly at the fibromuscular junction of isthmic segment with cervix. (5) After the unfolding has occurred, it is not possible to delineate the junction of corpus with isthmic segment by gross or microscopic examination of the uterine wall.

The question was raised whether it is proper to consider the isthmus of the nonpregnant uterus in its present light as a distinct, more or less autonomous entity, or whether it is best considered as part of the general muscular system of the uterus. A similar question may be submitted with respect to the pregnant uterus during the period covered by our specimens, for here, too, the isthmic musculature is seen to be a functional unit with the corpus. Both corpus and

cervix is refractory to the stimuli which elsewhere in the same organ give rise to such tremendous growth and contractile responses. Second, it is possible to understand the nature of the barrier which retains the products of conception within the uterus until their maturity. Third, a rational explanation is offered for the limitation of unfolding of the isthmic segment at the cervico-isthmic juncture. This is neither to deprecate nor to ignore the thesis of Stieve which was mentioned above, which very possibly may play a significant role in these occurrences. It is rather, to present an additional factor which is considered as of primary importance.

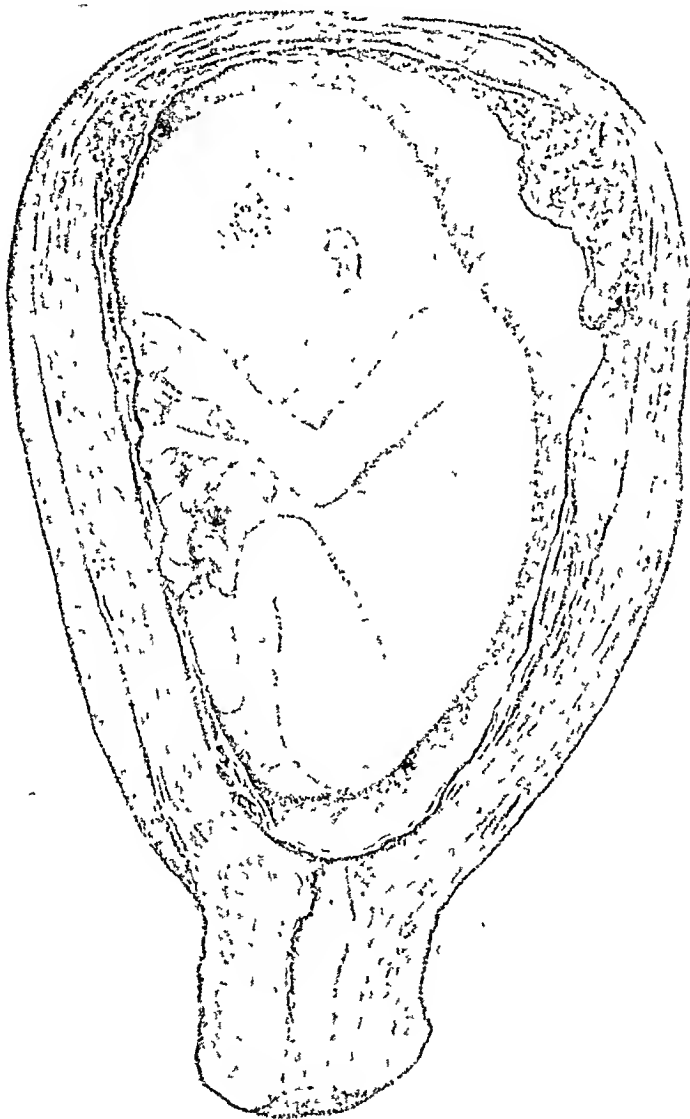


Fig. 10.—Frontal section, uterus No. 12. Pregnancy, fourteen weeks. ( $\times\frac{3}{4}$ )

No further light is shed upon the wonderful changes in the cervix during labor, except virtually to eliminate the possibility of their being due to muscular alterations.

Concerning the isthmus in the nonpregnant uterus, the following observations have been made: (1) in more than 45 per cent of the cases the lower

corpus, specifically, that portion of the corpus which lies between (a) the fibromuscular junction of cervix with corpus, and (b) the plane of the inferior level of the uterine cavity. It is recognized that in the nonpregnant uterus under certain circumstances neither (a) nor (b) may be sufficiently precise to allow the delineation of an isthmus, and that in any event the isthmus cannot be measured in terms of millimeters. Also, in pregnancy up to 3 months, the isthmus may be quite long; after 3 months it disappears entirely. The remaining alternative, of (b) lying superior to (a) is considered as not possible in a uterus which is not distorted by tumor growth.

In addition to its bearing upon the problems mentioned the thesis which has been presented also has direct implications with respect to the concept of the lower uterine segment. This correlation is beyond the scope of this paper, and will be presented elsewhere.

### Summary and Conclusions

In the nonpregnant human uterus the cervix is found to be composed predominantly of fibrous connective tissue, with an average of only about 15 per cent smooth muscle. The tissue superior to the cervix is composed predominantly of smooth muscle. The transition from fibrous to muscular tissue is generally quite abrupt; but it may be gradual, occurring over the space of 5 to 10 mm. In an attempt to study the isthmus uteri in terms of the original definition, it was found that its superior border (the anatomic internal os of Asehoff) cannot be precisely delineated; and in 45 per cent of the cases its lower border (the histologic internal os) is sufficiently vague that it too cannot be marked with precision. Also, the histologic internal os was found to be variable with respect to the constricted area known as the isthmie canal. It may lie within the constriction, or as far as 13 mm. below the constriction. Thus it is seen that the nonpregnant isthmus is an indefinite variable segment which is composed principally of smooth muscle, which is lined by a transitional epithelium, which is bounded below by the fibrous cervix, and which above blends imperceptibly with the remainder of the uterine musculature.

In the pregnant uterus the length of the cervix does not change significantly during early pregnancy. In the third month of pregnancy the isthmus elongates. This is considered as a hypertrophic response to pregnancy, and shows no significant difference from the similar reaction which occurs elsewhere in the muscularis. When the elongation occurs the products of conception are confined to the portion of the uterus which is superior to the isthmie canal. When the products of conception have enlarged sufficiently to require more space, the isthmie musculature unfolds to accommodate them and thus comes to make up a part of the wall of the ovum chamber. The unfolding is limited inferiorly by the fibrous cervix. The precise level at which the unfolding stops corresponds to the point at which the muscularis blends with the fibrous cervix, and is determined by the abruptness of the transition from muscular to fibrous tissue. In the case where the isthmus is unfolded it is not possible to distinguish the isthmie segment from the remainder of the corpus except that the wall may be thinner where the most dilatation has occurred.



isthmie segment manifest the same physiologic responses to pregnancy and are indistinguishable with respect to their muscular structure; differences in their morphology can be reduced to terms of the size of the products of conception, that is, whether they have enlarged sufficiently to utilize the available space.



Fig. 11.—Frontal section, uterus No. 6. Pregnancy, nineteen to twenty-two and one-half weeks. ( $\times\frac{3}{4}$ .)

Upon the basis of these findings, it is believed that the present designation of the isthmus as a separate structure, distinct from cervix and corpus, implies for this area special properties which it does not appear to possess. It is therefore suggested, first, that from both functional and anatomic standpoints the uterus be considered as composed of two major parts, cervix and corpus, according to whether the fundamental tissue is chiefly fibrous or chiefly muscular. Second, it is suggested that the isthmus uteri be recognized as a part of the

The idea that there is active growth in the isthmus when the product of conception begins to dilate the uterus is quite new, so far as I know, and well worth further study.

DR. EDWARD ALLEN.—The differences of opinion among authors quoted by Dr. Danforth are undoubtedly based on their interpretation of tissue also stained by differential stains. Those used by the author are probably more efficient and he has been very careful to provide controls. However, past experience should stimulate us to further corroborate his findings or strive to improve the techniques. This applies not only to staining methods, but fixation of tissue as well.

Differentiation of zones in a distensible organ on the basis of differences in size of lumen or muscular contraction rings may be a source of considerable error. Fixation of tissue with any fixative agent causes shrinking and changes in contour. Certainly muscle contraction of living or fresh tissue depends largely on the primary stimulus and the receptivity of the particular end organ. Muscle tissue adjusts itself readily to underlying structures, its attachments, and the tensions applied to it.

The tremendous changes in size, shape, and irritability which occur in the cells of the myometrium by hormonal influence and distention must in pregnancy be variable. In this connection it seems strange that Stieve should observe a gradual recession in the muscle tissue of the so-called isthmus from the second or third month of pregnancy to term, while we are fairly certain that the cells of the corpus are at the same time undergoing a marked progressive hypertrophy.

This histologic differentially stained fibromuscular junction of the uterine body with the cervix, which the author has demonstrated, seems quite definite, and to have only those variations in width and length as are found elsewhere when two organs are joined together. This zone of transition is just about as variable as that seen in the transition between the endometrium and the endocervix. The zone where these two mucous membranes join can be even more clearly differentiated by the staining methods used in this investigation.

I believe, as does the author, that the unfolding process which he refers to in the formation of the lower uterine segment is due to the fact that as far down as muscle tissue extends intrauterine tension and distention will use it for adaptation. However, it is very hard for me to visualize this as the only change when I examine a primipara vaginally before the onset of labor with the head very low in the pelvis and the edges of the external os almost paper thin.

This edge feels about as thick as the area of pure connective tissue just above the external os which is so definite in these histologic preparations and which Dr. Danforth refers to as embryonic or edematous connective tissue.

The sections of elastic tissue with their accompanying piece of monkey aorta convinces me of the relative sparseness of these fibers except those of the blood vessel aggregates. It also convinces me that residents and assistants are in error when at three o'clock in the morning they insist that a cervix which has been dilated to 7 cm. has contracted to admit only the tip of the examining finger.

DR. LOUIS RUDOLPH.—Dr. Danforth has presented the controversial site of the internal os which began with Bandl in 1875. The anatomic division of the corpus, isthmus, and cervix uteri of Aschoff in 1908 has been more or less accepted obstetrically. This indicates that the internal os is at the junction of the isthmus and cervix uteri.

We have demonstrated that the uterus of the carnivora and ungulata is divided into the horns and corpus and cervix uteri. The internal os is at the junction of the corpus and cervix uteri. In labor the horns undergo brachystasis (retraction) which is analogous to the human upper uterine segment; the corpus uteri undergoes meecystasis (stretching or thinning) which is analogous to the human lower uterine segment; and the cervix uteri undergoes circular and longitudinal meecystasis (dilatation and stretching or thinning, respectively) which is analogous to the "obstetrical" cervix uteri. Drs. Danforth and Ivy have demonstrated that the lower uterine segment of the monkey undergoes first brachystasis (I would rather refer

Because of these observations it is concluded that from both anatomie and functional standpoints the isthmus forms a unit with the remainder of the uterine musculature. Therefore, it is believed that the concept of the isthmus uteri as a separate, distinct entity should be eliminated and that, rather, the uterus should be considered as being composed of two major parts, corpus and cervix, according to whether the fundamental structure is chiefly muscular or chiefly fibrous. It is suggested that the isthmus be considered as part of the corpus (just as the fundus is part of the corpus), specifically, the part of the corpus which lies between (a) the level of the fibromuscular junction of cervix with corpus, and (b) the plane of the inferior level of the uterine cavity.

I am indebted to Dr. Earl T. Engle of the Department of Anatomy, College of Physicians and Surgeons, Columbia University, through whose interest and active help this study was made possible, and whose many kindnesses I wish to acknowledge.

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### Discussion

DR. GEORGE W. BARTELMER (by invitation).—Dr. Danforth has stated his case against dogmatic pronouncements in anatomy in very mild terms. His evidence is clear that the various subdivisions of the uterus recognized by the textbooks are highly variable so far as their proportions and their boundaries are concerned. In this they agree with most other characters of the female reproduction apparatus.

The findings as to the proportions of fibrous tissue and muscle in the cervix are new and unambiguous because adequate histologic methods were used. It is not sufficient to drop a uterus into a dish of formol and at some later time remove blocks of tissue, because the penetration of the fixative is very slow and the changes which occur in the interim prevent good differential staining. The method of infiltrating the uterus with the fixing fluid by means of hypodermic syringe is even better than perfusing the blood vessels. It not only gives prompt fixation, but makes it possible to cut sections thin enough to give a brilliant differentiation of smooth muscle and connective tissue when appropriate stains are used.

The incorporation of isthmus and corpus into a single functional unit so far as the myometrium is concerned is fully justified by the evidence presented. It is corroborated by the fact that the mucosa of the isthmus is a feebly developed but typical corpus mucosa, very different from that of the cervix.

removed, there is distortion first by partial contraction of the musculature, second, by the influence of external forces, as lying upon a flat surface or suspension in a fluid medium, and finally by fixation. Most significant is a knowledge of the general configuration prior to removal.

In answer to Dr. Allen's question concerning dilatation of the cervix in labor, the findings which I have outlined add little to our knowledge of this process. At least for the present, it appears necessary to fall back upon Stieve's explanation, although I cannot confirm all of his findings. It will be recalled that Stieve describes two groups of vascular spaces in the pregnant cervix, one at the level of the cervico-isthmic juncture, the second at about the level of the external os. In his specimens these spaces were so complex and so extremely congested that he refers to them as "erectile tissue." Stieve hypothesizes that effacement in early labor is due to the fact that the membranes are forced down through the internal os during a uterine contraction. As they are driven progressively lower into the cervical canal, the circumferential pressure against the vascular spaces causes them to be emptied of blood. When both groups of "erectile tissue" are emptied the cervix is thin, and completely effaced.

As to the connotation of the term "obstetrical internal os," I believe that in the primigravid uterus at term this refers to the junction of the cervical canal with the uterine cavity. Before effacement begins, I believe that the internal os is found at the level of the fibromuscular junction. With beginning effacement, which implies dilatation of the cervix from above downward, I believe that the original obstetric internal os is obliterated, and that the junction of cervical canal and uterine cavity gradually approaches the external os. Once the cervix is completely effaced, the obstetrical internal os has vanished.

In answer to Dr. Baer's question concerning the Hegar sign, at the stage when this sign can be elicited there is a considerable increase in vascularity, throughout. All will agree that the relaxed uterus of early pregnancy shows marked softening. At the time when the Hegar sign can be elicited, the products of conception are confined to the portion of the corpus which is superior to the isthmic segment. For purposes of illustration one may consider the conceptus at this stage as consisting principally of a noncompressible fluid. When one palpates the corpus one encounters this incompressible mass; when one palpates the cervix bimanually its fibrous content imparts a sense of relative firmness. But when the empty isthmic segment is grasped there is only the flabby uterine wall between the fingers; and this wall is easily and markedly compressible.

I believe that the demonstration of frequent abortion following high amputation of the cervix is evidence of the role of this portion of the uterus in retaining the products of conception. I do not know what the effects of previous high laceration would be, but suggest that the organ would retain this function unless its integrity were entirely disrupted.

With regard to the boundaries of the lower uterine segment, I believe this structure to be the portion of the uterine musculature which must undergo circumferential dilatation during labor, or during the uterine adjustments preparatory to labor. If the work of Dr. Ivy, Dr. Graham, and I may be applied to the human being, longitudinal elongation in this segment would appear not to be a factor in the thinning which is observed in normal unobstructed labor.

Concerning the percentage of smooth muscle at the various levels of the cervix: beneath the squamous epithelium of the portio vaginalis there is a zone of variable thickness which is composed entirely of loose areolar tissue. This zone merges with the substance of the cervix proper, which is composed of dense fibrous connective tissue. The actual percentages of smooth muscle here are difficult to assay, but they vary from virtually none to an estimated 40 or 45 per cent. Ordinarily the average is estimated as from 10 to 15 per cent. In many cases the portio supravaginalis contains rather more muscle than the portio vaginalis; but below the level designated as the fibromuscular junction the preponderance is fibrous tissue.

to this change as a temporary thickening, because brachystasis is a permanent thickening), and second, mecostasis (stretching or thinning).

The pregnant uterus is divided into a corpus and cervix uteri. The uterus after the fourth month is divided by the "obstetrical" internal os which is the region of Aschoff's histologic internal os. The corpus is made up of the upper and lower uterine segments and is separated from the "obstetrical" or Aschoff's cervix uteri by the "obstetrical" internal os. What is the so-called isthmus uteri and is it derived from the anatomic corpus or cervix uteri?

Before the complete obliteration of the internal os we find by intracervical palpation a sphincter-like structure, is this sphincter at or in the region of the anatomic or histologic internal os of Aschoff?

DR. GEORGE H. GARDNER.—As a result of examining these sections I have found it necessary to revise my previous concept of the relative amounts of smooth muscle and fibrous tissue in the cervix. Formerly I regarded the cervix as a fibromuscular organ, now I know that it is essentially a fibrous tissue structure. I regret greatly that the slides which he presented failed to demonstrate conclusively this preponderance of fibrous tissue in the cervix.

DR. JOSEPH L. BAER.—All of the obstetric clinicians in the audience are familiar with the Hegar sign. It has been my conception that the softening which we regard as the Hegar sign occurs in the isthmus uteri. I would like to ask whether there is a greater degree of hyperemia in the structures of the isthmus uteri in the early months of pregnancy than there is in the musculature just superior to the level of the anatomic os.

Second, all of us are familiar with the fact that a multipara whose cervix has been lacerated and unrepaired may nevertheless conceive and carry her pregnancy even though there is no structural support in the cervix up to the level of the constriction in the canal which is the anatomic os. If now this anatomic os represents what we have hitherto regarded as the final barrier to the corpus cavity, what then happens if the isthmus uteri, which is inferior to this anatomic os, is absorbed into the musculature of the growing corpus itself? Also, I am interested in knowing whether the essayist has formulated conceptions of his own concerning the parts of the uterus which eventually become the lower uterine segment. It has been my conception that the lower uterine segment is that portion of the uterus as a whole which encompasses the cervix, isthmus, and adjacent corpus, and not merely that part of the uterus which lies above the anatomic os.

Finally, the essayist devoted his attention quite properly to the well-known increasing preponderance of fibrous tissue over muscle tissue to delineate between corpus, isthmus, and cervix. In his observation of the endometrium and endocervix was he able to substantiate the dictum which has been handed down, that in the endometrium the direction of the lumina of the glands is inferior toward the cavity, whereas in the isthmus the direction of the lumina of the glands is superior toward the canal.

DR. DANFORTH (Closing).—With the exceptions noted in the body of the paper, all of the microscopic material was prepared by the laboratory of Dr. Earl T. Engle.

Dr. Bartelmez has referred to the finding of hypertrophy of the isthmic segment prior to its incorporation into the wall of the ovum chamber. I agree that many similar specimens must be studied before the changes here described may be considered as unequivocally typical. The obtaining of such specimens, particularly at this crucial stage, is difficult. Also, Dr. Allen has referred to the possibility of distortion by fixation, which is an extremely difficult factor to control. In the specimen I have described, I feel certain that the general contours after fixation were not greatly altered, since the uterus showed the same general shape when it was still in situ. This, of course, is an important consideration, and where specimens at this particular stage are concerned it is essential that one have accurate knowledge of the configuration before interruption of the blood supply. Precise measurements are misleading. They cannot be made in situ without undue manipulation, and, once the organ is

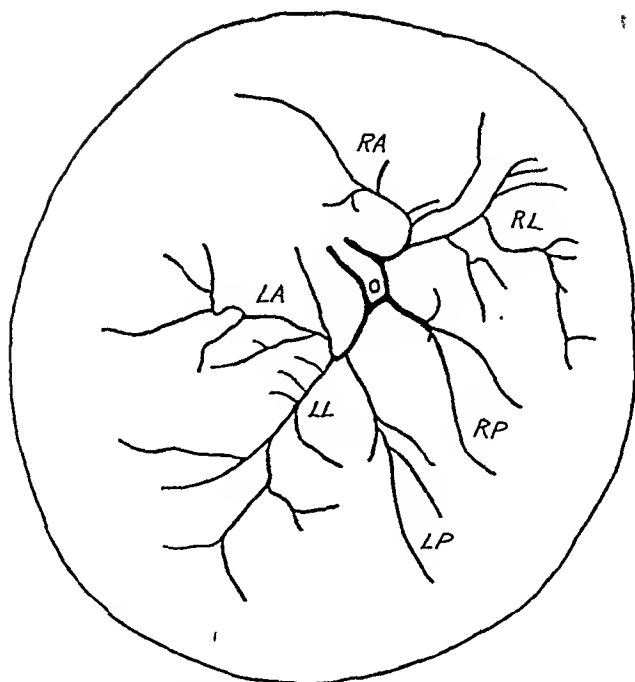


Fig. 1.—The vascular bed of the mature placenta. Note the cross anastomosis between the two umbilical arteries and the position of the umbilical vein anterior to the anastomosis. An anterior, lateral, and posterior branch of each artery supply approximately equal sextants of the placental area.



Fig. 2.—Outline drawing of a section through the Torpin ovum showing the amniotic duct in continuity with the trophoblast above and the amniotic cavity below. Note that the amniotic membrane forms the cephalic surface of the body stock, a position which it holds throughout pregnancy. Age, 13 days.

# THE AMNIOTIC DUCT AS THE KEY STRUCTURE IN THE DETERMINATION OF THE DIRECTION OF GROWTH OF THE HUMAN PLACENTA AND ITS ORIENTATION IN THE UTERUS

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GENERAL inspection of the human placenta has led to the opinion of its radial growth from a fixed center (Strassmann). This is based primarily upon the central insertion of the umbilical cord. The exceptions to this rule are, however, so numerous that they need no comment, being represented by all gradations from marginal to velamentous insertion. The point of reference forming the basis for most of the discussion is the body stock since this structure eventually materializes as the umbilical cord.

An examination of the vascular bed of the placenta shows, however, that it is bilaterally symmetrical with the right and left umbilical arteries distributed according to a definite basic pattern consisting of an anterior, lateral, and posterior branch on either side. Furthermore, right and left may be recognized by the fixed relationship of the umbilical vein which lies anterior to the cross anastomosis between the two arteries (Fig. 1).

That this condition is basic is indicated by the fact that it can be identified in the vesicle of the 3 mm. embryo, i.e., at the time the definitive vascular bed is first established.

This basic plan is more fundamental than that of Shordania, who, recognized a master, dispersed a special type of placenta based on the vascularity. Bacsich and Smout identify five types, all of which, however, may be seen to be bilateral.

In view of the fact that the body stock becomes invaded by an allantois, the human placenta has been generally interpreted as a precocious allantoic placenta in which the chorion has taken over the allantoic vessels. It is further assumed that the human allantois spreads out in the chorionic plate in a radial direction and simulates the condition noted in Tarius. For a complete phylogenetic development of the placenta reference may be made to the monograph of Mossman. The radial spread of the functioning allantois from the outer end of the umbilical cord in the lower forms naturally leads to the concept of a radial growth of the placenta about the umbilical cord insertion.

In the human being, however, the allantois remains a blind, atrophic stock extending forward only to the chorial plate at the time of vasculature is differentiated and established (Fig. 4). The steps in this process may be followed in the Mateer specimen and the Ingalls embryo.

## The Amniotic Duct

While the amniotic duct has been known for quite a period of time, it is only in recent years that its significance has become apparent. In the thirteen-

In contradistinction to the amniotic duct, the allantoic duct in man is a comparatively late development, making its appearance at 14 days in such a specimen as the Mollendorff's WO; extending well into the body stock in the Mateer specimen, and reaching as far forward as the amniotic duct in Ingalls' 1.38 mm. embryo at an age of 21 days (Fig. 4). A comparison of the last specimen with the Torpin ovum shows that there has been marked undercutting of the body stock from the chorial plate back to the region of the outer end of the amniotic duct, and this now becomes the outer end of the potential umbilical cord.

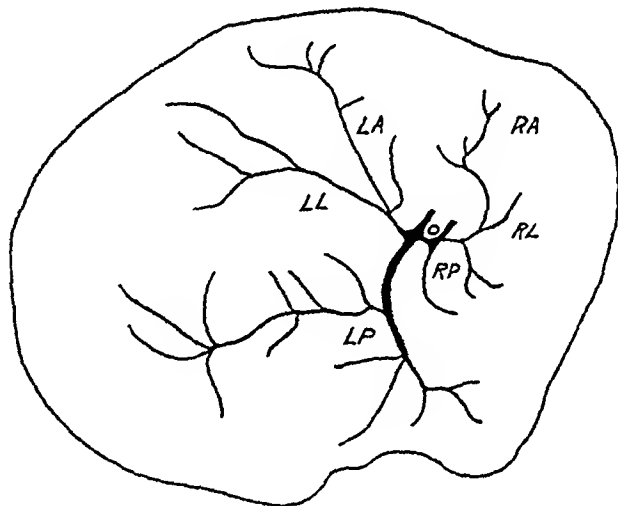


Fig. 5.—The vascular bed of a placenta showing asymmetric growth. The relative area supplied by the left artery is 2.26 as compared with the right, 1.07.

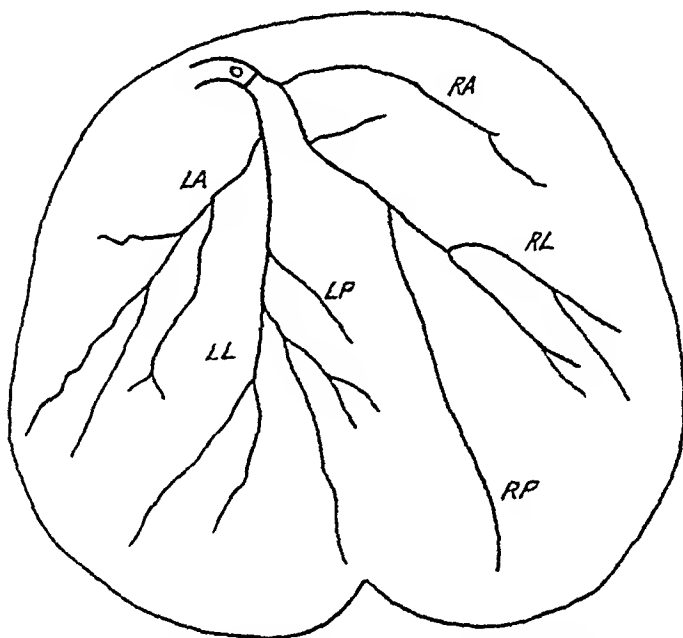


Fig. 6.—The vascular bed of a placenta with a marginal insertion of the cord and a notch indicating bilobation. Each artery supplies approximately the same area but the individual branches are highly variable.

This point becomes still further fixed as the vascular bed is established. We have been able to identify definitely the cross anastomosis between the two umbilical arteries in a 3 mm. specimen, a structure which is characteristic of the mature placenta.



day Torpin ovum (Fig. 2), it consists of a solid cord of cells in direct continuity with the Langhan's layer of the chorion above, and canalized at the lower end with the lumen opening into the amniotic cavity (Krafka). In other specimens it may be represented by an interrupted cord of cells (Heuser, Rock, and Hertig), or, as in the Ingall's specimen, persisting as a blind diverticulum from the cupula of the amniotic cavity. It is of course reminiscent of the strand of cells left along the raphe in those species where the amnion is formed by fusion over the embryonic shield.

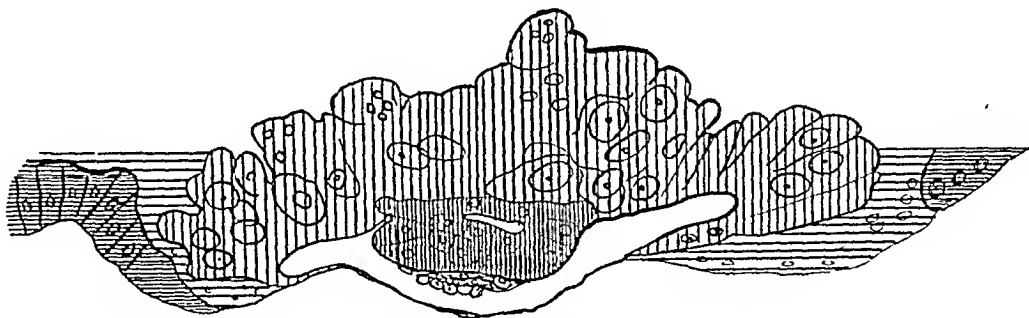


Fig. 3.—Outline drawing of a section of the Hertig-Rock seven-day ovum in the process of implanting in the endometrium. The massive cells are invading trophoblast, continuous at the margins of the crater, with the single layer of trophoblast at the abembryonic pole of the ovum. The endometrial epithelium has as yet not overgrown the ovum. The small cavity in the embryonic knob is the initial stage in the formation of the amnion. The larger cavity is the trophoblastic cavity. The yolk sac has not as yet formed.

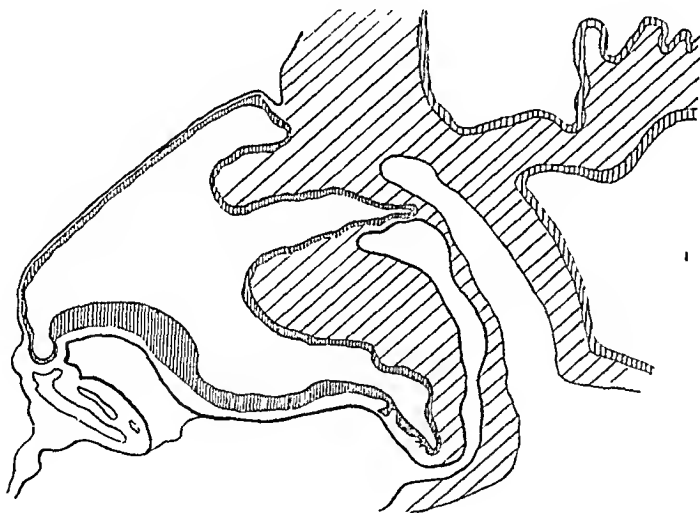


Fig. 4.—Outline drawing of a sagittal section of the Ingall's embryo, approximate age 21 days. Note the amniotic duct extending from the cupula of the amniotic cavity into the body stock. The allantois is the blind diverticulum from the hind gut invading the body stock as far forward as the amniotic duct. Undercutting of the body stock from the chorionic mesoblast has carried the distal end of the stock to the region of the amniotic duct.

The manner of amnion formation in the human being is by delamination. It is better described as a rearrangement of the cells of the embryonic knob about a central amniotic cavity (Fig. 3). The cells of the knob entering into this process are in continuity with the chorionic ectoderm at this point, and since these cells are the erosive cells, they mark the point of implantation of the ovum into the endometrium. This point is now well established by the seven- and nine-day specimens of Hertig and Rock. *Thus, the outer end of the potential amniotic duct underlies the implantation site.* We have found only one real exception to this among the many embryos described in the literature, namely, that of Florian and Hill in which implantation was effected by the abembryonic pole of the vesicle.

fundus; No. 3882 (Fig. 8) shows a marked growth toward the fundus with a simultaneous development of bilobation toward the cervix; No. 2578 (Fig. 9) shows major growth toward the cervix; No. 4054 with major growth toward the fundus; No. 1146 with oblique growth across the fundus and into the horn. Others follow in like order.

It is apparent then that from practically any point of implantation, growth of the placenta may be transverse, toward the cervix or toward the fundus. A low fundus implantation may by fundic growth result in a centrally placed placenta.

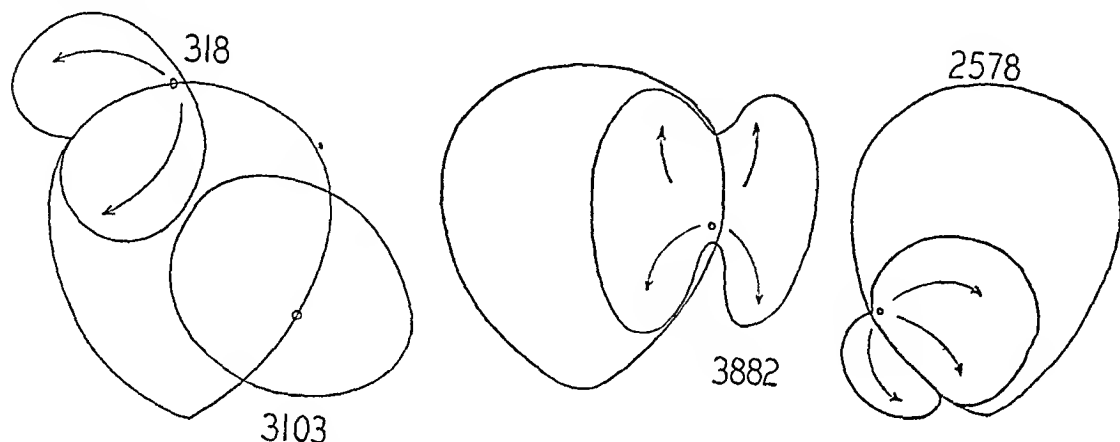


Fig. 7.—Drawing of figures from Torpin and Hart somewhat modified. 3103 illustrates the fact that implantation in the lateral sulcus of the endometrium does not necessarily produce bilobation. 318 shows bilobation from the dorsal sulcus. The position of the umbilical cord insertion shows that major growth was transverse, as indicated by the arrows.

Fig. 8.—Drawing from Torpin and Hart. 3882 illustrates the growth of the placenta both toward the cervix and toward the fundus.

Fig. 9.—Drawing from Torpin and Hart. 2578 illustrates the growth on the placenta toward the cervix from a point of low implantation as marked by the umbilical cord insertion.

### The Most Frequent Site of Implantation

Having established the cord insertion view as indicative of the point of implantation, all of the specimens in the Torpin collection were examined with the intent of determining the most frequent site at which the vesicle imbeds. There are 1,087 specimens available. Of these, 588 occur in the middle of the fundus; 36 and 23 are cornual, and 5 distinctly cervical, with 3 cervicolateral. We have divided a diagrammatic endometrium into 12 zones and have indicated the frequency of pregnancy in each (Fig. 10).

It is to be noted that the midline of the fundic zone is the most frequent, and philosophically the most favorable point of implantation. This mid-region of the fundus has long been postulated as the most favorable site for implantation. On phylogenetic grounds it is considered to represent the line of fusion of the two horns in bicornate uteri of the lower forms where abmesenteric implantation is common (Kearns). In contradistinction to this, a vascular view has been advanced. Lateral uterine arteries interanastomose in the midline segment only through minor branches. Here the arterial pressure is considered to be at its lowest and hence least likely to produce abortion and hence the most favorable site for implantation. The vascular hypothesis has been applied also to the cervix. The main arterial trunks enter the uterus at the junction of fundus and cervix, sending their principal branches upward and creating a high pressure zone in the descending cervical branches. Both these views are highly hypothetical and completely ignore the hydraulics of the spiral arteries, capable of completely nullifying any direct pressure gradients, by muscular contraction.

Through this series of steps, the implantation site may now be referred to identifiable structures on the mature placenta and the direction of growth of the placenta followed (Figs. 5 and 6). To make our thesis positive, we may recapitulate the following steps: (1) the normal implantation site overlies the embryonic knob; (2) the amnioembryonic cavity arises by rearrangement of cells in the knob; (3) the amniotic duct marks the continuity between amnion and implantation trophoblast; (4) by undercutting the outer end of the body stock reaches the outer end of the amniotic duct; (5) the anastomosis between the developing umbilical arteries fixes the outer end of the body stock as it becomes the core of the umbilical cord, preventing such a postulate as "cord rotation." Hence the *placental insertion of the cord marks the normal implantation site*.

### Direction of Growth of the Placenta

With these points established we may now examine the placenta to determine the direction of its growth and its orientation within the uterus, bearing in mind the necessary steps to convert a small ellipsoidal vesicle completely covered with villi into a massive discoidal structure. We are currently working on the histologic features of this problem, but in this paper we will deal only with the gross features of the process, as represented primarily in the bilaterally symmetric bilobate placentas. Torpin and Hart have published figures of all the bilobates occurring in their collection. They also indicate the point of insertion of the umbilical cord on each placenta and the orientation of the placenta in the uterus. From this data it is possible to determine the direction of growth.

It is surprising that in most of the grossly bilobate placentas the umbilical cord insertion falls on the line dividing the structure into halves. Of the Torpin collection this point is situated at or near the center of the line in 22 cases. In 13 cases the point falls near the margin on the central line and away from the notch separating the two lobes. In four cases the insertion is on the central line and near the end of the notch. Since the insertion point marks the original implantation site, the major direction of growth in the second class has been anterior; in the third class, posterior. In the first class the direction of growth has been in the direction both anterior and posterior with a delayed separation in the direction of growth in the two lobes.

Since the use of the terms anterior and posterior may be confusing to some, it should be pointed out that they really represent the cardinal embryologic directions of cephalad and caudal which may easily be determined by recourse to the topography of an embryo such as Torpin, where the body stock (potential umbilical cord) supports the caudal end of the specimen.

One must, of course, before proceeding further with the argument, consider the commonly held view as to the cause of bilobation of the placenta, namely, that it occurs from the extension by growth over the sulci between the anterior and posterior surfaces of the endometrium. This concept may readily be disposed of by (1) the fact that bilobation may occur in a placenta occupying only one wall, and (2) some placentas may extend across the sulcus from one wall to the other without showing bilobation (Fig. 7, No. 3103 Torpin). Bilobation is really the result of the adaptation of the growing villi to the maternal vascular bed.

### Orientation of the Placenta in the Uterus

Being able to determine the direction of growth of the bilobate placenta from the relation of the umbilical insertion point to the central line, we may now examine the orientation of the placenta in the uterus. In the Torpin series (Fig. 7), No. 318 shows placental extension transversely across the

## Implantation Sites in Some Known Human Ova

We have superimposed the implantation sites of some known human ova upon the triangle of a diagrammatic endometrium (Fig. 11). Seven of these are in the midline, three are slightly to the right, three to the left, and one cornual. The data are too few to give any correlation between the site of implantation and the migration period between ovulation and implantation. It may be noted, however, that the Hertig-Rock seven-day specimen was ovulated from the left side and implanted on the right. One of our twins is a high midline, the other low. It would seem that uterine tone and local peristalsis might be of more significance in localizing implantation sites than either of the hypotheses in the previous section. Data on this point are needed and should be recorded as part of the routine description of embryos in the future. One conclusion is certain—the midline frequency is real and not due to equalizing growth of the placenta in the later stages.

## Conclusions

1. The human placenta is bilaterally and not radially symmetrical.
2. The right and left umbilical arteries show an interanastomosis at the point of insertion of the umbilical cord on the placenta.
3. Beyond this they each show an anterior, lateral, and posterior branch, and then relative area distribution indicates the direction of major growth.
4. The right and left sides of the placenta may be determined by the position of the umbilical vein which lies anterior to the interanastomosis.
5. This ground plan is present in the 3 mm. embryo.
6. The amniotic duct, underlying the implantation trophoblast, marks the site of the definitive umbilical cord insertion on the placenta, and at the same time the implantation site.
7. The direction of growth of the placenta from this point may be determined by examination of bilobate placentas, and is shown to be (1) anterior, (2) posterior, (3) lateral; and oriented transversely across the uterus, toward the fundus, or toward the cervix.
8. Taking the umbilical cord insertion point as that of implantation, the most frequent implantation site is in the midline of the fundus. Data from the Torpin collection are given.
9. Census of known implantation sites for young human ova shows this line to be established early, and not due to compensatory growth of the placenta at a later date.

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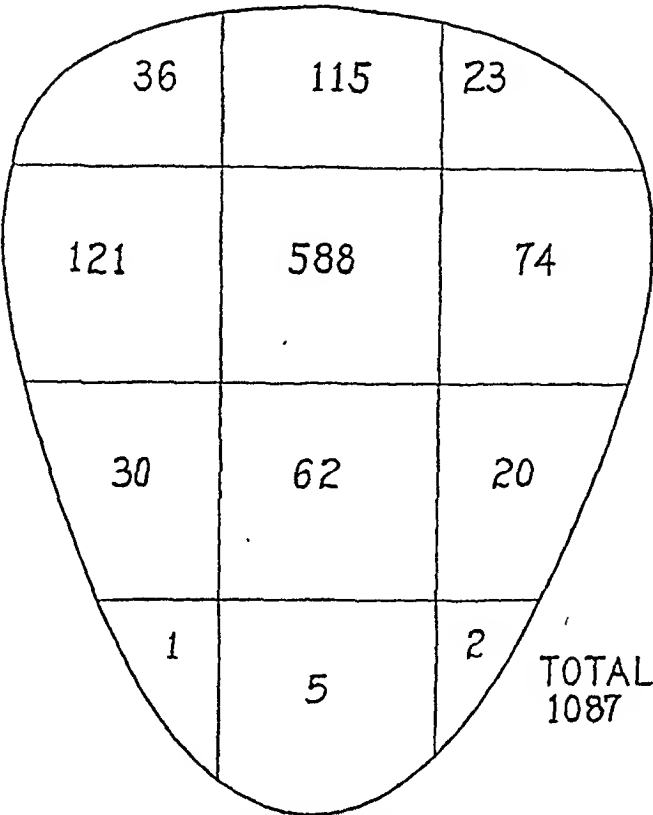


Fig. 10.—Diagram of the uterus subdivided into 12 zones and showing the frequency of implantation in each as indicated by the umbilical insertion point. The data are from the unpublished work of Dr. Richard Torpin.

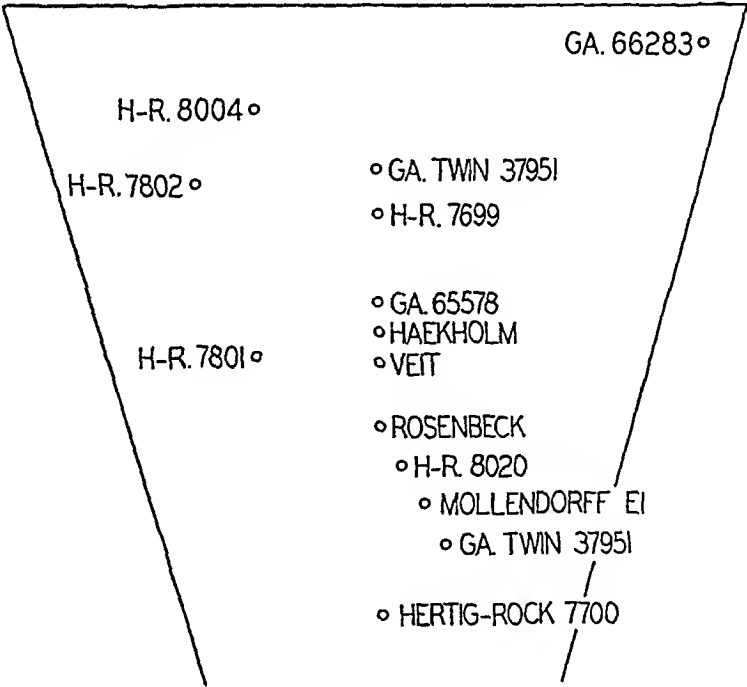


Fig. 11.—Diagram of the endometrial triangle showing the position of the implantation sites of various young human embryos. Six are from the reported work of Hertig and Rock, four from our own material. Note the distance between implantations of our twins, GA 37951. Hertig-Rock 8020, with a corpus luteum in the left ovary, implanted on the right side.

*Laboratory.—*

1. *Rh typing*: Our method differs slightly from that used by other workers in this field.<sup>5, 13-15, 17-20</sup> The cells, usually obtained from the blood clot, are washed once in physiologic saline and then resuspended in this medium to form a 2 per cent suspension. One drop of the suspension is added to two drops of diagnostic serum (anti-Rh<sub>0</sub> and anti-Rh', respectively), previously diluted and neutralized against the A-B-O<sup>16</sup> agglutinins, in a test tube 7 to 10 by 75 mm. The mixture is agitated and then incubated for one hour in a water bath at 37° C. The reactions are then read with the aid of a hand lens (magnification 14×), and any doubtful readings are checked microscopically.

2. *Rh-antibody determinations*:<sup>\*</sup> Our methods of testing for the presence or absence of Rh agglutinin differs only in minor details from those used by other investigators.<sup>5, 13-15</sup> The type O Rh-positive erythrocytes used as antigens, when testing for the presence of antibodies, are selected from those giving strongly positive reactions with both diagnostic sera (i.e., Rh<sub>0</sub> and Rh'). They are washed once and resuspended in normal saline solution in a concentration of 2 per cent. Each serum is tested with two group O Rh-positive cell suspensions and two group O Rh-negative cell suspensions. Two drops of the unknown serum are placed in each of four test tubes 7 to 10 by 75 mm. To each of these tubes is added one drop of the known cell suspension. The mixtures are agitated and then incubated for one hour in a water bath at 37° C. At the end of this time each tube is very gently shaken, the suspension is spread on a slide, examined under the low power of the microscope, and the results recorded. If the two control suspensions (Rh-negative cells) show no agglutination, the results of the two test suspensions (Rh-positive cells) are averaged and recorded as -, ±, 1+, 2+, 3+, or 4+ Rh agglutinin.

Each serum is tested concurrently for the presence or absence of blocking antibody.<sup>13, 15, 21-27</sup> To one drop of the unknown serum, in a test tube 7 to 10 by 75 mm., is added one drop of the same Rh-positive cell suspensions as are used in the test for Rh agglutinins. The mixtures are shaken and then incubated for one hour at 37° C. in a water bath, at the end of which time one drop of anti-Rh<sub>0</sub> serum is added to each test tube. In order that the final concentration of known anti-Rh<sub>0</sub> will be the same as that used in the standard Rh typing test, a dilution of anti-Rh<sub>0</sub> serum of twice the usual concentration must be used in order to compensate for the fact that only one-half the quantity of this known serum is used in the blocking antibody test. The test tubes are again shaken and incubated further for two hours. The test suspensions are examined microscopically under the low power, and the results with the two antigens are averaged and reported as: 4+ agglutination—no blocking present; 3+ 2+, 1+ agglutination—partial blocking present; and ± and no agglutination—complete blocking present.

*Statistical.—*

1. *Definitions*: The results of the antibody studies on Rh-negative mothers are grouped into four categories, classified according to the Rh-characteristic and clinical outcome of the infant: Group I, normal Rh-negative infants; Group II, normal Rh-positive infants; Group III, Rh-positive infants exhibiting signs of sublethal hemolytic disease of the newborn; and Group IV, Rh-positive infants with frank hemolytic disease of the newborn.

Group I is a random sample which includes data from all the women who were delivered of Rh-negative infants, with the exception of two women, the data on whom so exaggerated the effect of the other 61 cases, that it was considered justifiable to exclude them from the random sample and to discuss

\*The methods described are the ones in use in this laboratory in 1944-1945, when these data were collected.

**THE CLINICAL SIGNIFICANCE OF Rh ANTIBODIES (Rh  
AGGLUTININS AND BLOCKING ANTIBODIES) IN  
THE SERA OF Rh-NEGATIVE MOTHERS;  
A STUDY OF 179 CASES\***

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SINCE the recognition of the importance of the Rh factor<sup>1</sup> in the etiology of hemolytic disease of the newborn,<sup>2-12</sup> much interest has been focused on the antibodies which are formed in response to the Rh-antigen. From the laboratory, data have been accumulated in regard to the genetics, biochemistry, and immunology of these antigen-antibody reactions, despite the fact that their clinical significance is not clearly understood. The obstetrician would like to know the meaning and the clinical interpretation of variations in demonstrable antibodies found in the sera of pregnant Rh-negative women. What significance can be placed on the quantity of these antibodies and on the time of their appearance? What conclusions can be drawn from the fluctuations in their intensity of reaction? What is the meaning of the agglutination or blocking reaction, and is there an interrelationship between these responses to immunization? The following material is presented in the attempt to establish a correlation between the laboratory data on women immunized by the Rh factor and the clinical findings in their offspring.

**Methods**

*Clinical.*—A specimen of blood and a data sheet from every patient on her first visit to the Obstetrics Clinic of the University of California Out-Patient Department is routinely sent to the blood typing laboratory to be pedigreed for blood group and Rh-characteristic. Similar material was also obtained from the offices of several obstetricians in private practice. If a sample is found to be Rh negative, the serum from that specimen and from specimens taken on each subsequent antepartum visit to the clinic or office are tested for the presence or absence of Rh antibodies. In addition, an attempt is made to obtain and pedigree samples of blood from the husbands and living children of these Rh-negative women in order to give the obstetrician an interpretation of the potential significance of the laboratory findings in the patient *before* parturition. Samples of blood from the umbilical cords of the infants born to all these patients (both Rh negative and Rh positive) are sent routinely to the laboratory for typing, and the results of these tests are reported immediately to the nursery so that infants who might be the victims of iso-immunization may be carefully watched for signs of disease. Specimens for postpartum antibody study are taken from each Rh-negative mother just before she leaves the hospital and on each subsequent postpartum visit to the clinic or office.

\*Supported by a grant from the Columbia Foundation, San Francisco.

Laboratory and Clinical Data

*Group I.*—Theoretically, there is no likelihood of demonstrating Rh antibodies in the serum of an Rh-negative woman, whose fetus in utero does not possess the Rh characteristic, unless she had been previously immunized to the Rh factor by pregnancy or transfusion. In this series of 61 Rh-negative women bearing Rh-negative fetuses, isolated antepartum appearances of Rh agglutinin were demonstrable in 15 per cent of the cases. The majority of reactions were of very low titer, only one showing as much as 2+ agglutination. Post partum, one of the 34 cases studied showed Rh agglutinins.

*Group II.*—Some evidence of antibody formation might be expected in Rh-negative women delivered of Rh-positive infants, even though the babies show no clinical signs of hemolytic disease of the newborn. Of 78 women within Group II, tested ante partum for the presence of Rh agglutinins, 31 per cent showed isolated positive reactions.

Rh agglutinins were demonstrable post partum in the sera of 29 per cent of 48 women. The average amount of antibody present was definitely higher than that found ante partum. Of the women whose sera gave positive reactions post partum, five cases demonstrated a considerable amount of Rh agglutinin in their sera, and a study of the babies born to these women revealed the interesting data presented in Table I. Three of these infants may be considered to have been clinically normal, but two presented symptoms which suggest that there had been some interaction between the maternal Rh agglutinin and the fetal tissues. In both cases these findings were noted in the children of primiparous women.

*Group III.*—The antibody findings in Group III, that of Rh-negative women who were delivered of Rh-positive infants diagnosed as having subclinical

TABLE I. CLINICAL FINDINGS IN A GROUP OF APPARENTLY NORMAL RH-POSITIVE INFANTS BORN OF RH-NEGATIVE MOTHERS WHOSE RH-AGGLUTININ TITERS SHOWED AN APPRECIABLE INCREASE POST PARTUM

CASE	PARITY	DEMONSTRABLE RH-AGGLUTININS IN SERA OF MOTHERS		CONDITION OF CHILD
		ANTE PARTUM	POST PARTUM	
H. P.	Multipara	23 weeks ± 19 weeks ± 1 week ±	2+	Normal as far as known
M. G.	Primipara	17 weeks - 7 weeks -	2+	Normal at birth, but on subsequent physical examinations: act. 1 mo. Nothing of note act. 2½ mo. Nothing of note act. 3½ mo. Liver 1 to 1½ cm. below costal margin act. 4½ mo. Spleen palpable act. 5 mo. Liver 1½ cm. below costal margin
E. S.	Multipara	16 weeks - 14 weeks - 4 weeks -	3+	Normal as far as known
D. S.	Multipara	10 weeks - 8 weeks - 4 weeks 1+	3+	Normal as far as known
L. T.	Primipara	10 weeks - 4 weeks ± 2 weeks 2+	4+	Child premature Act. 10 days: 1 NRBC/100 leucocytes Spleen tip palpable Discharge diagnosis: Questionable hydrocephalus



them separately. These 61 cases of Rh-negative women who were delivered of normal Rh-negative infants represent a heterogeneous group of subjects who may have had, and in some cases did have, the opportunity to develop iso-immunization in pregnancy due to the Rh factor.

Group II includes studies made on the random sample of Rh-negative women who were delivered of normal Rh-positive infants. Again the data on all such women are included, with the exception of four unusual cases which are discussed in a separate publication.<sup>28</sup> This random sample of Rh-negative women who were delivered of clinically normal Rh-positive infants should represent the first step in the mechanism of the iso-immunization of pregnancy.

Group III includes the results of the antibody studies made on all Rh-negative women who were delivered of Rh-positive infants who (a) were clinically diagnosed as having "subclinical hemolytic disease of the newborn," (b) were clinically or pathologically diagnosed as having "questionable hemolytic disease of the newborn," or (c) exhibited at least three of the following abnormalities:

1. More than five nucleated red blood corpuscles per 100 leucocytes
2. Sustained jaundice
3. Spleen 1 cm or more below the costal margin
4. Petechiae or other evidences of the bleeding tendency
5. Liver 1 cm. or more below the costal margin
6. Less than 100 per cent of hemoglobin

This group should then represent the next stage in the evolution toward complete iso-immunization as it is manifested by severe disease in the newborn infant.

Group IV consists of data obtained from all Rh-negative women who were delivered of infants diagnosed by the physician as having hemolytic disease of the newborn and on whom there were at least two antepartum serologic observations. The infants of this group, whose blood samples were typed, were all Rh positive. There were three stillborn and macerated infants whose erythrocytes were so badly damaged that it was impossible definitely to establish their Rh status. This group then should represent an advanced stage in the iso-immunization of pregnancy due to the Rh factor.

2. "*Trend*" charts: The term "average titer value" is based on the intensity of the agglutination reaction rather than on the actual titer of Rh-antibodies in the serum. Each point represents the average intensity of reaction of all the observations made within that particular span of time. The antepartum observations of antibody titer were grouped according to equal time intervals of either two, three, or four weeks. The data were presented in this manner in order to maintain first the same trend as was evidenced by the weekly averages, and secondarily to increase the number of observations per unit in order to smooth the curve of incidence. The postpartum observations were grouped in unequal intervals, the first point representing the average of all the observations made within the first week following parturition, the second point the second week, and the third point the span from the third week through the ninth week, the mean point falling in the sixth week post partum.

3. "*Case*" charts: Each bar represents the average amount of antibody found in the serum when tested against two antigens, as described above. The clinical histories were obtained directly from the hospital and clinic records of the Department of Obstetrics or through the kindness of the collaborating private physicians. While the "trend" charts include all the cases studied, the "case" charts include only some of the representative instances of each type.

showed isolated low titers (2+ or less) of Rh agglutinins ante partum. Under ordinary circumstances women within this group would represent a heterogeneous sample in regard to previous sensitization to the Rh factor, because it is not always possible to determine the Rh characteristic of the husband or to elicit histories of previous pregnancies, abortions, or miscarriages. In three instances where it was possible to determine the past history of Rh-negative women bearing Rh-negative children and demonstrating persistent Rh-agglutinin titers ante partum, it was shown (Fig. 1) that the antibody titers were not fortuitous. Two of the patients (M. N. and P. V.), both multiparous women, probably represent examples of the "carry-over" phenomenon. Case M. N. had a past history which suggested previous iso-immunization of pregnancy. At the age of 11 years she was given a transfusion which was followed by a severe febrile reaction. The chances are that she had received Rh-positive blood and thus became sensitized. Case P. V. maintained a constant strong Rh-agglutinin titer throughout pregnancy. The intensity of antibody reaction observed in the serum of this woman is remarkable, because her last exposure to the Rh antigen by pregnancy must have taken place several years previously, and, as far as is known, she never received a transfusion. Since pregnancy must have been the means of sensitization, and since the Rh agglutinin which she developed was of high titer, it is surprising that apparently none of her offspring showed evidence of hemolytic disease of the newborn. During the present pregnancy the Rh-agglutinin titer was 4+ in the undiluted serum, but failed to give more than a  $\pm$  reaction in serial dilutions.\* Cases of the "carry-over" type would be expected to maintain a constant trend of antibody ante partum<sup>30-32</sup> and this expectation is fulfilled in the cases of M. N. and P. V. The third case illustrated in Fig. 1 (D. P.) does not comply with any of the usual observations found in instances of the "carry-over" phenomenon. The patient was a primiparous woman, and, as far as was known, had never received any transfusions, so that the opportunity of previous sensitization to the Rh factor seems to have been lacking. Another unusual feature is that this subject demonstrated a dropping, rather than a constant, trend of Rh-agglutinin titer ante partum, findings similar to those observed in some of the women who bore infants diagnosed as having hemolytic disease of the newborn. No explanation of this unusual case can be offered except the rather extravagant hypothesis of the existence of an Rh-positive twin which died in utero and was subsequently resorbed.

In summary, the presence of Rh antibodies in the serum of Rh-negative women bearing Rh-negative children has little or no clinical significance. In cases where the previous obstetric or transfusion history is unknown or willfully concealed, or where the precise Rh characteristic of the husband cannot be determined, it is obvious that the serologic test is of dubious value in predicting the outcome of the child in utero.

\*The observation has been made by McIvor and Lucia\* that in cases where the Rh agglutinins are maintained in the serum from previous episodes of immunization, the antibodies can rarely be demonstrated in serial dilutions beyond 1:2 or 1:4, although they give reactions of marked intensity in the undiluted serum.

hemolytic disease of the newborn, would be expected to differ rather markedly from those of Group II, in which the infants were clinically normal. Of the 17 women in Group III tested for Rh agglutinin ante partum, the sera of 29 per cent (five cases) gave only an isolated  $\pm$  reading, which figure is about the same as that found in Group II. However, a much greater proportion of cases (35 per cent) show either single observations of high titer or repeated observations of low titer of Rh agglutinin. The relationships between the Rh agglutinin and blocking antibody in this group are shown in Figs. 9 and 10. All of the Rh agglutinin titers of 1+ or more were observed during the last eight weeks of pregnancy, even though only 63 per cent of the total number of tests on this group were made within this period of time. This association of Rh-agglutinin titers in late pregnancy is greater than would be expected to occur by chance alone. Only 10 of the 17 cases were tested post partum, and, of these, 50 per cent showed some Rh agglutinin. Demonstrable Rh antibodies, especially blocking antibody, seem to have been lost rapidly from the sera of the women who bore infants only mildly affected with hemolytic disease of the newborn. This is in direct opposition to the findings among the women who bore infants more severely diseased.<sup>5, 10, 15, 30-32</sup>

Until quite recently, the significance of subclinical hemolytic disease of the newborn did not receive proper recognition in the literature. The findings in this study support the observations made by others<sup>5, 31, 37</sup> that the occurrence of physiologic jaundice of the newborn in itself is probably not an indication that iso-immunization has occurred. Although the majority of infants who are affected by the Rh antibodies transferred from the maternal serum present clinical evidence of disease within the first twenty-four hours after birth, a few cases have been reported<sup>31, 38</sup> which show no clinical evidence of disease until several weeks after birth (cases T. B. and C. S.).

*Group IV.*—The sera of all twenty cases in Group IV, that is, Rh-negative women bearing children afflicted with frank hemolytic disease of the newborn, contained varying amounts of demonstrable Rh agglutinin at some time prior to delivery; the majority, however, developed a marked reaction to the Rh antigen. Finding at least a trace of Rh agglutinin ante partum in the sera of all women delivered of definitely affected infants supports the statements of Levine<sup>4, 7</sup> that even though Rh agglutinin may not be demonstrable after delivery in mothers of affected infants, this does not mean that the antibody may not have been demonstrable at some time during pregnancy. Although, on the average, the Rh agglutinin titer rose following delivery, a smaller percentage of cases gave positive reactions for this antibody post partum than ante partum. Rh agglutinin was found post partum in the sera of only 89 per cent of these women, an incidence which agrees closely, however, with that of Boorman and co-workers<sup>5</sup> and Ginson,<sup>37</sup> but which is somewhat higher than that of other investigators.<sup>4, 6, 7, 30</sup> Eighty-five per cent of the postpartum antibody tests were made within the first two months, and another 12 per cent during the third and fourth months following parturition. The antepartum incidence of blocking antibody was not as high as that of Rh agglutinin, although 11 (69 per cent) of the 16 cases tested gave evidence of some blocking. The total incidence of positive postpartum blocking antibody reactions was slightly more than that found ante partum, 80 per cent of the 15 cases having some blocking antibody present in their sera following parturition.

### Discussion

*A. Occurrence of Antibodies in Rh-Negative Women Delivered of Normal Rh-Negative Children.*—The majority of women in this group, as would be expected, failed to reveal any sensitization to the Rh factor. Of 61 women, 9

TABLE II. PERCENTAGE INCIDENCE OF ISOLATED OCCURRENCE OF RH-ANTIBODIES IN THE SERA OF RH-NEGATIVE WOMEN WHO BORE CLINICALLY NORMAL RH-POSITIVE INFANTS (GROUP II)

ANTE PARTUM		
AMOUNT OF ANTIBODY DEMONSTRATED	RH AGGLUTININ (78 CASES)	BLOCKING ANTIBODY (22 CASES)
±	17%	0
1+	11%	4%
2+	2%	18%
3+	0	0
4+	0	0

POST PARTUM		
AMOUNT OF ANTIBODY DEMONSTRATED	RH AGGLUTININ (48 CASES)	BLOCKING ANTIBODY (13 CASES)
±	17%	0
1+	2%	8%
2+	4%	8%
3+	4%	0
4+	2%	0

TABLE III. THE INCIDENCE OF ISOLATED ANTEPARTUM OCCURRENCE OF RH ANTIBODIES OF LOW TITER AMONG RH-NEGATIVE MOTHERS WHOSE INFANTS DEVELOPED HEMOLYTIC DISEASE OF THE NEWBORN

		GROUP III (RH-NEGATIVE WOMEN DELIVERED OF INFANTS WITH SUBCLINICAL HEMOLYTIC DISEASE OF THE NEWBORN)	GROUP IV (RH-NEGATIVE WOMEN DELIVERED OF INFANTS WITH FRANK HEMOLYTIC DISEASE OF THE NEWBORN)
Cases followed 9 or more weeks before delivery	With reference to Rh agglutinin only*	88% of 8 cases	15% of 13 cases
	With reference to Rh agglutinin and blocking antibody	60% of 5 cases	0% of 10 cases
Cases followed less than 9 weeks before delivery	With reference to Rh agglutinin and blocking antibody	50% of 6 cases	8% of 13 cases

\*The cases in this category are displayed primarily because of the presence of Rh agglutinin. Some of them had not been studied for the presence of blocking antibody, in which case it is obvious that the Rh agglutinin might have been masked. Fifteen per cent represents two cases, one of which demonstrated blocking antibody ante partum and the other a low titer of blocking antibody post partum. Therefore, it is possible that these two cases in Group IV may have had more than isolated instances of Rh agglutinin.

women whose infants were Rh negative was higher before than after parturition may lend support to this idea. These three phenomena then may account for some, but certainly not all, of the isolated positive antibody reactions.

A discussion of Rh agglutinin and blocking antibody reactions of low intensity, some apparently nonspecific, may seem to exaggerate their importance, but the point is that they *do* occur ante partum, and consideration must be given to their possible significance in predicting the effect on the infant. Reactions of 1+ or 2+, unless repeated on several occasions, may be interpreted as having no clinical significance. Comparison of these figures with the incidence of similar isolated ante partum occurrences of Rh antibodies of low titer among the Rh-negative mothers whose infants *were* clinically affected yields interesting and rather startling results. In Table III are given data which demonstrate that at least subclinical hemolytic disease of the newborn may

*B. Incidence of Isolated Occurrence of Antibodies.*—In Group II (Rh-negative women who bore normal Rh-positive infants), Rh antibodies occurred as isolated instances in 30 per cent of 78 cases (Table II). These data demonstrate that the incidence of Rh antibodies is greater among Rh-negative mothers bearing Rh-positive infants than among Rh-negative mothers bearing Rh-negative infants. Our data show that small amounts of Rh antibodies are demonstrated ante partum in a relatively large percentage of Rh-negative women subsequently delivered of normal Rh-positive infants, an incidence higher than that found by other workers in the field.<sup>3, 33-35</sup> This may be due in part to the fact that these women were tested more frequently during pregnancy.





CASE	OBSTETRICAL HISTORY	WEEKS ANTE-PARTUM			DELIVERY	CHILD	WEEKS POST-PARTUM	
		16	11	6			1	6
MN	GRAVIDA IV, PARA I I induced abortion at 4 mos. II FTND-kernicterus-RH+ III spontaneous abortion IV present HUSBAND IS RH-POSITIVE		■	■ ■ ■	Spont			
DP	GRAVIDA I, PARA 0 I present	■	■ ■ ■ ■ ■		Spont		-	
PV	GRAVIDA VI, PARA IV I FTND } 1st marriage II FTND } III FTND } 2nd marriage IV Abortion at 2 mos } Present V FTND } marriage VI Present } PRESENT HUSBAND IS RH-NEGATIVE	■	■	■	Spont		■	
<b>LEGEND:</b> ANTI-RH: ■ BLOCKING ANTI BODY: ▨ NONE: □ TRACE: + + ++ +++ ++++ CHILD:  Normal								

Fig. 1.—A study of Rh-antibody titers in Rh-negative women who have been delivered of Rh-negative infants.

Several factors should be considered in the discussion of the cause of isolated positive antibody reactions. The first possibility lies in technical error. Although this may have occurred, it is not likely, since Rh-negative controls were set up with each serum, and because the final reading in each observation is the average reaction of the serum with two Rh-positive antigens. Another factor, whose influence is difficult to measure and which may account for some spurious positive reactions, is the anamnestic phenomenon<sup>29</sup> or "carry-over" titer—one which was developed previously by transfusion, or, in multiparous women, by prior pregnancies, and which bears no relation to the immediate fetus in utero.<sup>18, 30-32</sup> A third possibility is that there may be some nonspecific factor of pregnancy itself which produces false positive or anamnestic reactions. The fact that the incidence of positive Rh-agglutinin tests among the

D. *The Clinical Significance of the Occurrence and Trend of Antibodies.*—

1. *The Rh agglutinin:* A summary of our observations of the average trends of Rh-agglutinin titers found in pregnant Rh-negative women is given in Fig. 2. As would be expected, both theoretically and by studying the data presented above, the average antepartum Rh agglutinin titer observed in Rh-negative women bearing clinically normal infants (Groups I and II) is practically negligible excepting for a very slight agglutinin response in Group II.

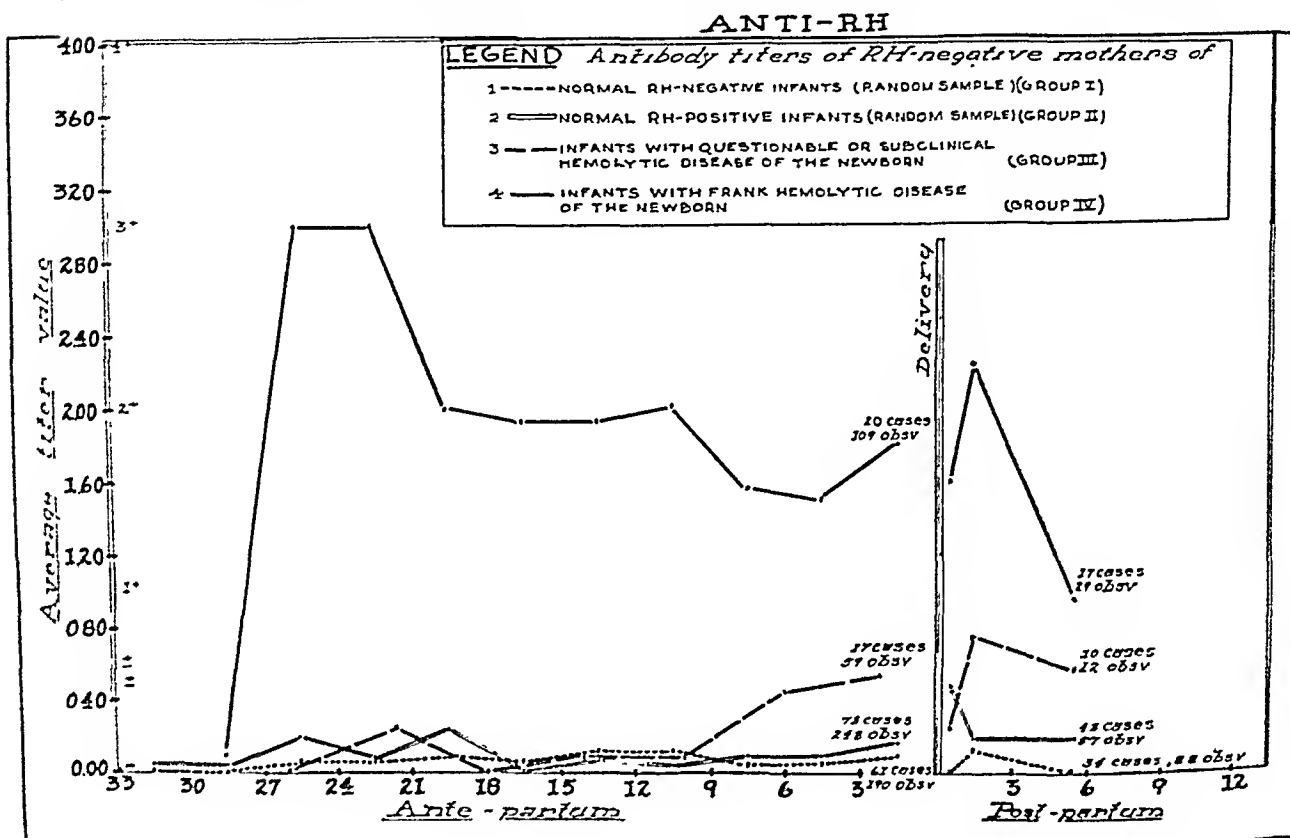


Fig. 2.—The average trend of Rh antibody in pregnant Rh-negative women with reference to time and the clinical outcome of the infant.

Post partum, the average titer in Group II rises slightly, while that of Group I falls. The Rh-agglutinin titer among the women of Group III (bearing Rh-positive infants mildly afflicted with hemolytic disease of the newborn) is not demonstrable until about ten weeks before parturition, and, although the intensity of the reaction is never very marked, an appreciable rise does occur, and it continues until delivery.<sup>39, 44</sup> Post partum, the antibody titer reaches its maximum intensity in the second week and then begins to drop. The trend of Rh-agglutinin titer of women in Group IV (bearing infants with frank hemolytic disease of the newborn) portrays a dramatic increase in antibody titer when compared with that observed in the women of Group III. Although the early peak in the Rh agglutinin trend line of women in Group IV may be exaggerated by observations made on patients with "carry-over" titers, the antibodies in the sera of women in this group seem to drop gradually as pregnancy progresses. After delivery, there is a rise in the Rh-agglutinin titer

occur in the offspring of women who present only small isolated amounts of antibody ante partum. By contrast the incidence of isolated antibody in Rh-negative women bearing infants with frank hemolytic disease of the newborn is quite small. In these groups, the cases considered were only those which, having been tested at least three times prior to delivery, failed to show more than an isolated low titer of Rh antibody. Of the women who were delivered of infants only mildly affected with hemolytic disease of the newborn (Group III), a surprisingly *large* proportion presented an antepartum picture of little or no demonstrable immunization to the Rh factor. Among the women whose infants were severely affected with hemolytic disease of the newborn, only a few, as would be expected, showed evidence of slight iso-immunization. Therefore, it would seem that the possibility of significant immunization cannot be overlooked in cases where Rh agglutinin or blocking antibody are only occasionally detected in the sera.<sup>35</sup>

In summary, it may be stated that the isolated occurrence of Rh antibody of low titer may be significant under circumstances where evidence of immunization occurs early in pregnancy or where blocking antibodies mask the Rh agglutinins.

*C. Relation of Parity to Antibody Formation.*—As would be expected, antibody formation occurred more often among the multiparous than among the primiparous women. In Group II, the incidence of Rh agglutinin is higher in the multiparous than in the primiparous women, however, a statistically significant difference<sup>36</sup> could not be demonstrated, probably because of the smallness of the sample. In Group III, none of the four primiparous women showed Rh agglutinin ante partum, while 11 of the 13 multiparous women showed at least an isolated positive test for this antibody. This is a statistically significant difference of occurrence. In Group IV, all women showed at least a trace of demonstrable Rh agglutinin at some time prior to delivery.

In the total group of 48 primiparous women who were delivered of Rh-positive infants, twelve showed antibody formation. Of these, only one bore an infant diagnosed as having frank erythroblastosis fetalis, and this occurred in a woman who was diagnosed as having had syphilis. In the total group of 67 multiparous women who were delivered of Rh-positive infants, 43 showed antibody formation. Of these, 11 bore infants diagnosed as having evidence of subclinical erythroblastosis fetalis, and 19 bore infants diagnosed as having frank erythroblastosis fetalis. These data bear out the statement that not only are the antibodies encountered more frequently in multiparous women, but that their intensity interpreted in terms of disease in the infant is infinitely greater.

In summary, it is important to test for Rh antibodies in Rh-negative women, regardless of parity, especially since sensitization to the Rh factor, through transfusion or other means, may have occurred in the distant past and have been forgotten. Occasionally a subject is encountered who may be easily immunized and who, during the course of the first pregnancy, would be capable of developing antibodies of an intensity sufficient to harm the product of conception.

similar to that of the Rh agglutinin. The trend lines of Groups I and II are similar for both antibodies, but the trend of blocking antibody titer in Group III differs markedly from that of the Rh agglutinin for this group. The early peak in the blocking antibody curve of Group III does not represent a true rise in the average titer, because there were few observations made during early pregnancy on this group, and one observation of a high titer of blocking antibody, made on a patient who had been previously sensitized, exaggerated the average titer value. Except for this variation, the blocking antibody, like the Rh agglutinin, fails to appear in the sera of these women until about the tenth week before parturition, at which time a marked rise in titer occurs. Ante

## BLOCKING ANTIBODY

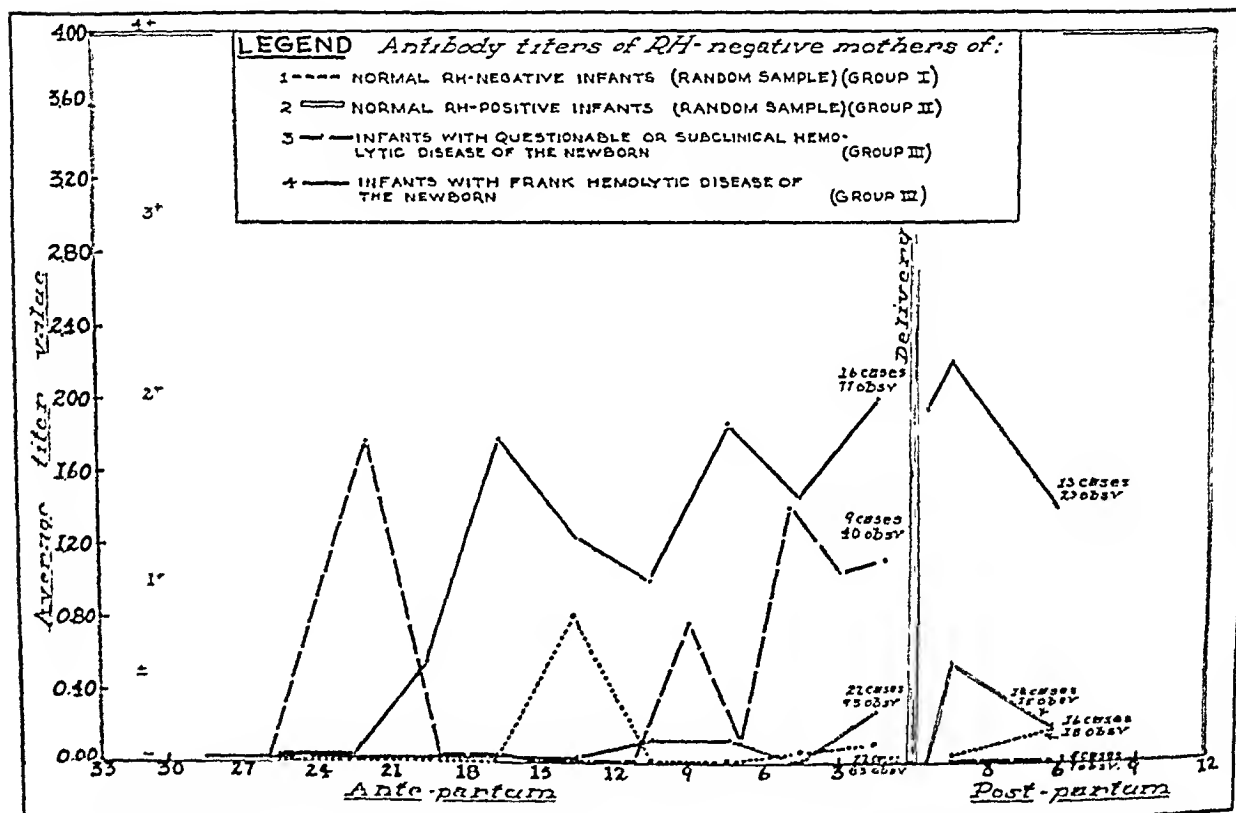


Fig. 3.—The average trend of Rh antibody in pregnant Rh-negative women with reference to time and the clinical outcome of the infant.

partum, the average titer of blocking antibody in the women of Group III is somewhat higher than the average titer of Rh agglutinin. Post partum, the situation is reversed—the Rh-agglutinin titer rises, while that of the blocking antibody becomes imperceptible. Among the women of Group IV, blocking antibody appears later in pregnancy than does Rh agglutinin. Ante partum, the titer of blocking antibody rises, and reaches at parturition about the same average level of intensity as that of the dropping trend of Rh agglutinin. Post partum, the trend lines of the two antibodies are very much alike. On the whole, the women of Group IV show less blocking antibody than Rh agglutinin in their sera, whereas the opposite is true of Group III.



which reaches its peak in the second postpartum week. This finding is in agreement with the observations made by other investigators in the field.<sup>5-7, 15, 30-32</sup> The progression of iso-immunization in pregnancy is well illustrated by these data—not only is there progression in intensity of antibody reaction, but also progression in relationship to time. In the aggregate, the women of Group I show practically no Rh-agglutinins at any time, those of Group II have demonstrable antibodies only after parturition, those of Group III show significant titers of antibody late in pregnancy, while the women of Group IV have high titers of Rh agglutinin in their sera early in pregnancy.

A few women exhibited an antepartum titer of Rh agglutinin which rose to a peak at delivery, then either dropped again or remained at approximately the same level during the first few weeks following parturition. There were also a few instances in which the antepartum titer trends were not apparent, due to the fact that antibody studies were not started until late in their pregnancies.

The sera of three women (two illustrated in Fig. 11), who later developed markedly high titers of Rh agglutinin, were originally tested before any demonstrable antibody had developed. One (M. Mc.) gave a negative reaction for this antibody in the twenty-eighth week before delivery, and when tested again in the twentieth week prior to delivery, had developed a 4+ titer of Rh agglutinin. Another woman (F. P.), whose serum gave a negative reaction in the thirtieth week before parturition, had developed a 3+ titer when tested again fifteen weeks before delivery. The third case (E. M., not illustrated) had no Rh agglutinin when tested fifteen weeks before term, but four weeks later she showed the first trace of agglutinin which subsequently rose to a titer of 2+ at delivery. From these observations, one would judge that Rh agglutinins may not be demonstrated by the twenty-eighth week before parturition, but that a strong titer of the agglutinin can be developed at least by the twentieth week prior to delivery. The sera of two women (one illustrated) gave Rh-agglutinin reactions of high titer in the twenty-first and twenty-seventh antepartum weeks, respectively, but in both the obstetric histories strongly suggested that they had been previously sensitized to the Rh antigen.

A constant trend of Rh agglutinin titer ante partum occurred with about the same frequency as the dropping trend. It may be that some of these cases would have shown a rising or dropping titer if antibody studies could have been made earlier in pregnancy, but, as far as known, the titer of Rh agglutinin was fairly constant in these women prior to delivery. The majority of these cases also maintained a constant titer during the first weeks after delivery, so that the antibody picture presented cannot be readily distinguished from the "carry-over" phenomenon found in a woman, previously immunized, but harboring an Rh-negative fetus. In one case, however, the titer did rise immediately after parturition, and in another it rose about six weeks later.

2. *The blocking antibody:* In Fig. 3 are illustrated the average trends of blocking antibody titer observed in women of the four groups. The progression of intensity of reaction and of time of appearance of this antibody is

not illustrated) was it possible to establish the approximate time of appearance of the blocking antibody. Case B. D., at twenty-one weeks' ante partum, had no demonstrable antibody, but at seven weeks' ante partum the blocking antibody reaction was 2+, and the titer continued to rise until delivery. This was one of the rare cases in which the antepartum titer of blocking antibody exhibited a rising trend. Case E. M. gave negative reactions when tested for the presence of blocking antibody during the fifteenth, eleventh, and seventh weeks before parturition. When tested during the fourth week ante partum, a 3+ blocking antibody titer was obtained, and this was maintained at a constant level through the second week post partum. These cases suggest that the blocking antibody, at least in a form detectable in the laboratory, does not appear until relatively late, whereas Rh agglutinin seems to be demonstrable quite early in the course of pregnancy. These data and conclusions, which are not in accord with Wiener's hypotheses,<sup>15</sup> gain further support from the observations made on the women in Group II. In this group of cases, which should represent the first stage in the development of iso-immunization, the incidence of positive Rh-agglutinin tests is appreciably higher than that of positive blocking antibody tests.

Three possible antepartum trends (rising, dropping, and constant) were observed in the blocking antibody studies made on the women of Group IV. An example of a rising trend has been given above (B. D.), but this type occurred infrequently. Likewise, cases exhibiting blocking antibody titers which dropped before delivery were only occasionally observed, one such case (B. J.) being illustrated in Fig. 5. The fact that intrauterine death of the fetus occurred, as closely as the physician could judge, at about the time that the blocking antibody titer dropped, makes this case especially interesting, although there may be no true cause and effect relationship between these occurrences. The titer of blocking antibody in the serum of this patient rose following parturition. In another case (not illustrated) which exhibited a dropping antepartum trend, the titer failed to rise after parturition.

The great majority of the cases in Group IV exhibited a constant antepartum titer of blocking antibody, varying from repeated negative reactions to repeated findings of 3+ and 4+ titers. In most cases exhibiting a constant trend, the blocking antibody titers were maintained at the same level through parturition and the first two weeks post partum. In one case (M. Q.) the antibody had disappeared completely within the second week post partum. When the serum was tested again eleven weeks post partum, the blocking antibody had regained the original antepartum level. In general, those women whose sera contained a high titer of blocking antibody during pregnancy continued to show a high titer after delivery with the exception of two cases, M. Q. (Fig. 5) and M. D. C. (not illustrated). The blocking antibody titer of the latter dropped from 3+ to negative before delivery and remained negative on the postpartum examination.

In Figs. 4, 5, 11, and 12, some representative cases of Group IV are illustrated with respect to both the Rh agglutinin and blocking antibody findings.

In Figs. 4 and 5 some cases of Group IV are illustrated in terms of their antepartum titers of antibodies. As a rule, the blocking antibody, once it has been developed, seems to be maintained at a fairly constant level, although this impression may be due to the fact that few tests were made early in the course of pregnancy. The earliest positive blocking antibody reactions were

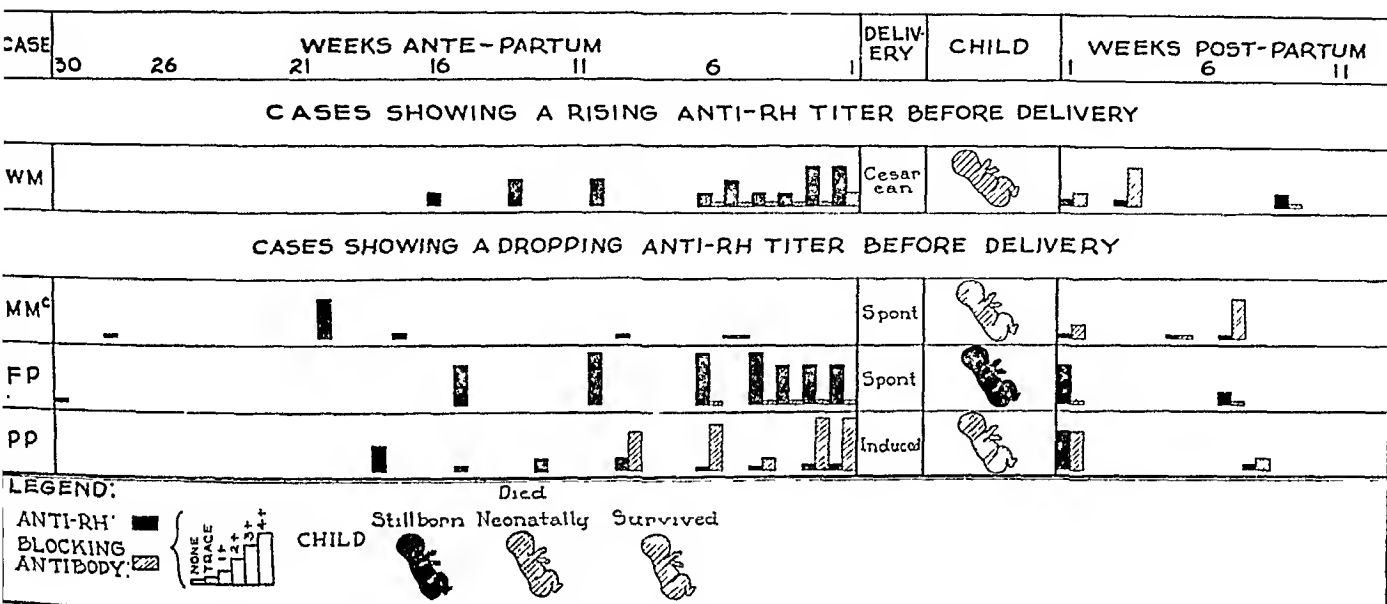


Fig. 4.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by antepartum trend of anti-Rh). Part "A."

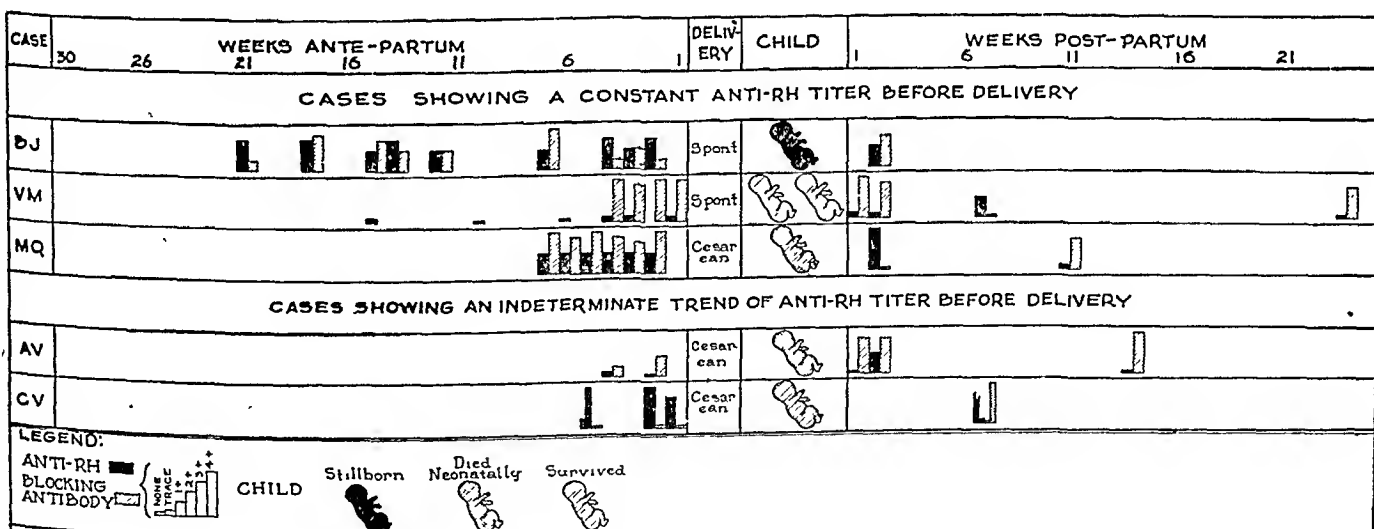


Fig. 5.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by antepartum trend of anti-Rh). Part "B."

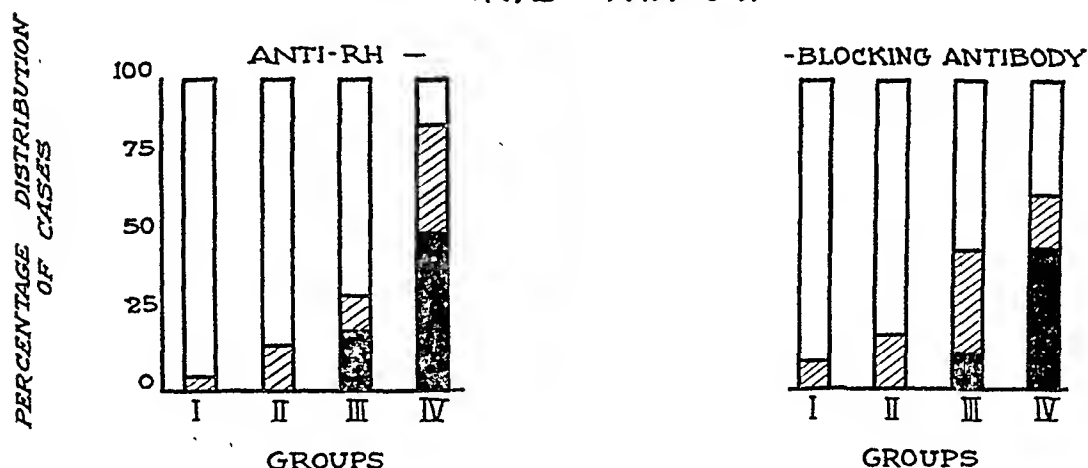
found in the twenty-first, twelfth, and ninth weeks before delivery (B. J., M. D. C. [not illustrated], and P. P.); however, the obstetric histories of these patients suggest previous iso-immunization, so that they may represent examples of the "carry-over" phenomenon. In only two cases (B. D. and E. M.,

one of these was tested at frequent intervals beginning in the twenty-seventh week ante partum. The graphic proof that a dropping antepartum titer of Rh agglutinin is not necessarily due to the appearance of blocking antibody can readily be seen from these illustrations. Similarly, a rising Rh-agglutinin titer is not necessarily due to the loss of demonstrable blocking antibody, which fact is borne out in the case (W.M.) illustrated. Six of the seven women whose antepartum trend of Rh agglutinin was constant exhibited also a high titer of blocking antibody. This might be interpreted to mean that blocking antibody can hide the true trend of an Rh-agglutinin titer, but readings of the latter as high as 3+ were observed in the presence of a fairly strong titer of blocking antibody, so that it does not appear that the result of the Rh agglutinin test can be completely submerged by the blocking antibody. However, there are cases (W.M., V.M., M.Q.) in which postpartum tests showed a higher Rh-agglutinin titer when the blocking antibody titer dropped or disappeared altogether. It is interesting that this interchange rarely took place before parturition. On the other hand, some Rh-agglutinin titers rose ante partum or post partum without any variation in the amount of demonstrable blocking antibody in the serum (W.M., P.P., A.V.). In Figs. 11 and 12 the same cases are arrayed according to the amount of blocking antibody in the sera ante partum. Cases M.Me. and W.M., two of the six which exhibited little or no blocking antibody in the sera during pregnancy, showed an increased amount following delivery, and one of these had a corresponding decrease in Rh-agglutinin titer. It is not possible to state with certainty that the apparent postpartum rise of blocking antibody was due to the absence of the fetus which may have been absorbing the antibody prior to parturition. This has been advanced as a possible explanation of the above phenomenon. On the average, the women who demonstrated high titers of blocking antibody ante partum showed Rh-agglutinin titers of lesser intensity than those who had little or no blocking antibody. This again suggests that in the laboratory the presence of blocking antibody may partially submerge the appearance of the Rh-agglutinin. Aside from the associations already discussed, a study of the data presented in Figs. 4, 5, 11, and 12 does not warrant general conclusions concerning the interrelationships which might exist between the two types of Rh antibodies.

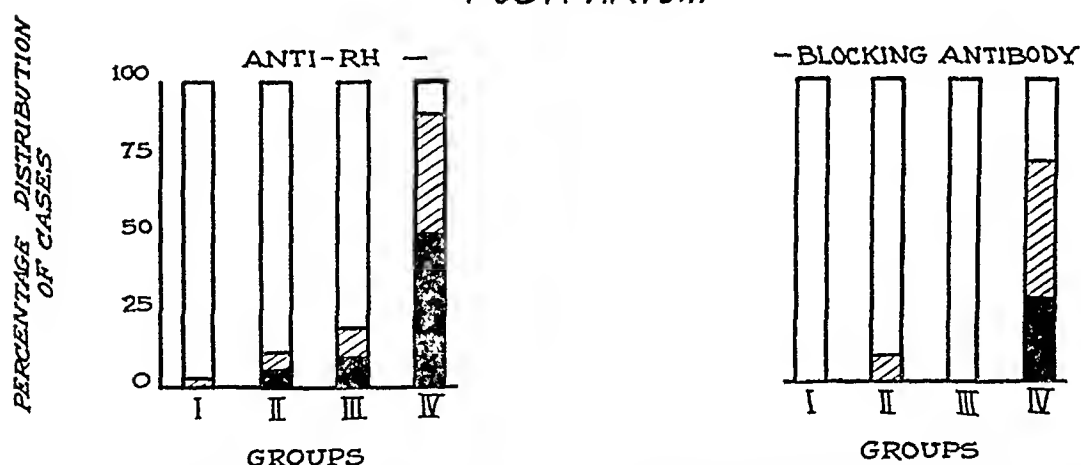
3. *The clinical significance of antibody trends:* Table IV and Fig. 6 give the comparison of the incidences of antibody titers among these four groups of Rh-negative mothers. The expected progression of laboratory evidence of sensitization is clearly shown, although it is rather surprising that the spectacular changes in distribution occur between the women of Groups III and IV rather than between those of Group II, in which the Rh-positive infants were clinically normal, and those of Group III, in which the Rh-positive infants exhibited symptoms of subclinical hemolytic disease of the newborn. These findings suggest that when it becomes possible to study a large sample of women delivered of infants suffering from hemolytic disease of the newborn, a finer classification of the group in terms of clinical symptoms in the infant

These data show no striking interrelationships between the two forms of response to the Rh antigen. Few generalizations can be made from Figs. 4 and 5, where the data are arrayed according to the antepartum trend of Rh-agglutinin titer. Cases B. J. and M. Q. illustrate that surprisingly high titers

### ANTE PARTUM



### POSTPARTUM



**LEGEND:**  low titer of antibodies  moderate titer of antibodies  high titer of antibodies

Group I Rh-negative mothers of normal Rh-negative infants.

Group II Rh-negative mothers of normal Rh-positive infants.

Group III Rh-negative mothers of infants with subclinical hemolytic disease of the newborn.

Group IV Rh-negative mothers of infants with frank hemolytic disease of the newborn.

Fig. 6.—Relationship of maternal Rh antibodies to clinical outcome of the infants of four groups of Rh-negative women.

of both antibodies may be demonstrable at the same time in the serum of a patient, although as a rule one or the other type of antibody predominates. While every woman in Group IV had at least a trace of demonstrable Rh agglutinin in her serum at some time prior to delivery, three of those tested never showed any blocking antibody, either before or after parturition, and

TABLE IV. PROGRESSION OF ISO-IMMUNIZATION IN PREGNANCY DUE TO THE RH FACTOR

ANTE PARTUM									
RH AGGLUTININ					BLOCKING ANTIBODY				
HIGHEST OBSER- VATION OF ANTIBODY	PER CENT DISTRIBUTION OF CASES				HIGHEST OBSER- VATION OF ANTIBODY	PER CENT DISTRIBUTION OF CASES			
	GROUP I 61 CASES	GROUP II 78 CASES	GROUP III 17 CASES	GROUP IV 20 CASES		GROUP I 22 CASES	GROUP II 22 CASES	GROUP III 9 CASES	GROUP IV 16 CASES
Low titer (-, ±)	95	85	70	15	Low titer (-, 1+)	91	82	56	38
Moderate titer (1+, 2+)	5	15	12	35	Moderate titer (2+, 3+)	9	18	33	18
High titer (3+, 4+)	0	0	18	50	High titer (3½+, 4+)	0	0	11	44
POST PARTUM									
RH AGGLUTININ					BLOCKING ANTIBODY				
HIGHEST OBSER- VATION OF ANTIBODY	PER CENT DISTRIBUTION OF CASES				HIGHEST OBSER- VATION OF ANTIBODY	PER CENT DISTRIBUTION OF CASES			
	GROUP I 34 CASES	GROUP II 48 CASES	GROUP III 10 CASES	GROUP IV 18 CASES		GROUP I 16 CASES	GROUP II 13 CASES	GROUP III 5 CASES	GROUP IV 15 CASES
Low titer (-, ±)	97	88	80	11	Low titer (-, 1+)	100	92	100	27
Moderate titer (1+, 2+)	3	6	10	39	Moderate titer (2+, 3+)	0	8	0	46
High titer (3+, 4+)	0	6	10	50	High titer (3½+, 4+)	0	0	0	27

to delivery. However, this was a frequent finding among the women in this series whose infants were afflicted with hemolytic disease of the newborn. Two of the cases (E. K. and M. Mc., illustrated) are of special interest in that the Rh agglutinins became imperceptible before delivery. If these women had been tested only during the last trimester, there would have been no indication of sensitization until after the birth of the infant. Although it has been suggested, but not proved, that this type of titer trend may be due to the absorption of the antibody by the fetus in utero, theoretically, an apparently falling Rh-agglutinin titer ante partum might be due to the rise of blocking antibody in the serum of the patient. In one case (F. P.), however, no blocking antibody was ever demonstrable in the serum, either before or after the Rh-agglutinin titer began to drop. The serum of another woman (M. Mc) was tested for the presence of blocking antibody only in the fifth week before delivery, at which time the demonstrable Rh agglutinin had disappeared completely, but there was no blocking antibody in her serum. The result of antibody studies on these two patients introduces a valid objection to the hypothesis that the reciprocity of Rh-antibody titers is the only explanation of this phenomenon. Within the first two weeks following parturition, such dropping titers either remained on a constant level or rose again. None showed a further drop until six to eight weeks after delivery. It is noteworthy that none

may show a more pertinent relationship when correlated with the serologic manifestations in the mother. In general, following parturition, blocking antibody would seem to be lost more rapidly than Rh agglutinin from the sera of all sensitized Rh-negative women. Again the rapid loss, post partum, of demonstrable Rh antibodies, especially blocking antibody, from the sera of the women in Group III is shown. Another point of interest is the antepartum difference between Groups III and IV in reference to the ratio of blocking antibody to Rh agglutinin. Group III shows relatively more blocking and less Rh agglutinin, whereas the relationship in Group IV is just the opposite. From the study of these four groups it becomes apparent that while there are definite differences when the cases are studied in the aggregate, it is frequently impossible to classify individual cases in regard to the future well-being of the fetus *in utero*.

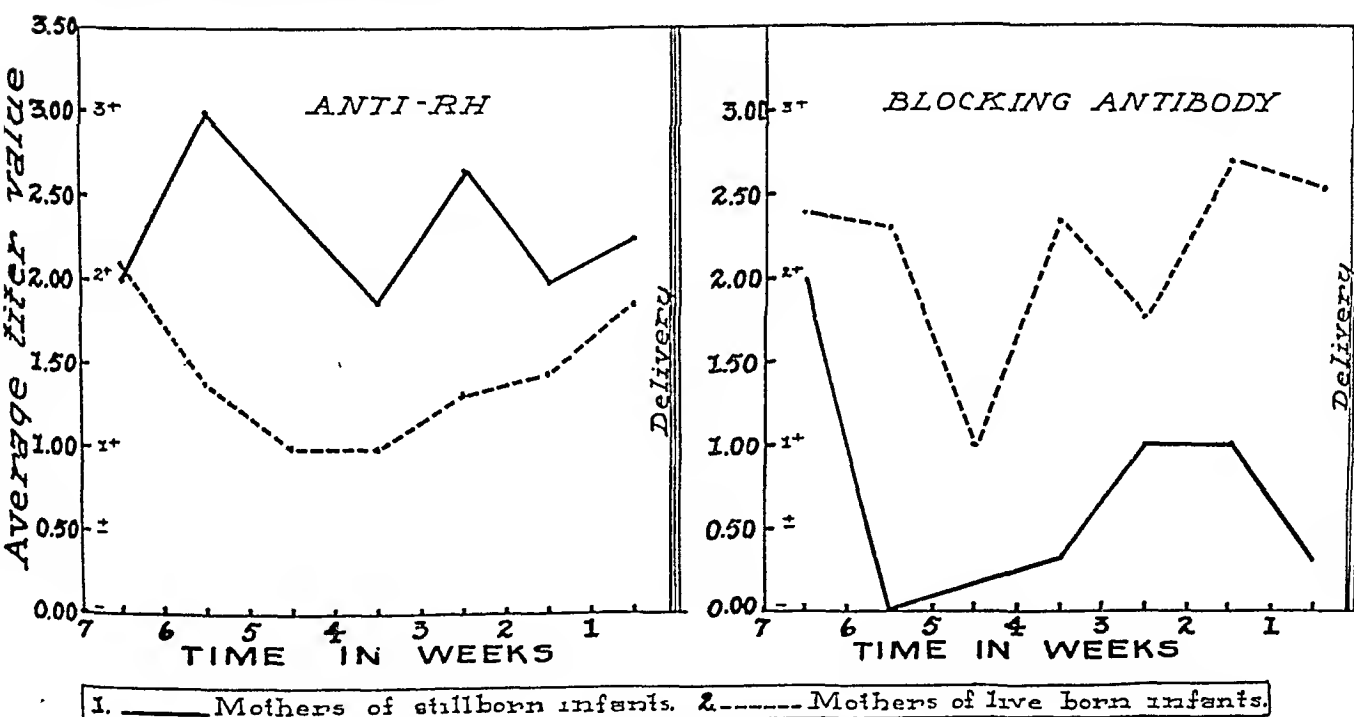


Fig. 7.—A comparison of the average Rh-antibody titers observed during the last seven weeks of pregnancy in women of Group IV whose infants were stillborn, and in women of Group IV whose infants were alive at birth.

A more detailed inspection of some of the representative cases in Group IV may give further insight into the clinico-laboratory correlation of Rh sensitization. A study of the antibody titers in these women yields more definite information than a similar analysis of the women in Group III. In Figs. 4 and 5 the Rh-agglutinin titers are illustrated, arranged according to their antepartum trends. Actual examples are given of each of the three theoretical possibilities, a rising, a constant, or a dropping trend. Other investigators<sup>30-32, 39</sup> have noted the antepartum occurrence of a rising or constant titer of Rh agglutinin in women who were subsequently delivered of erythroblastotic infants, but no reference has been made to an antibody titer which drops prior

maternal sera, the greater the possibility that hemolytic disease of the newborn will occur.

*E. Relation of Blocking Antibody to Rh Agglutinin.*—A subject frequently discussed in the field of iso-immunization of pregnancy is that of the nature of the blocking antibody, its relation to the Rh agglutinin, and its apparent "protective or destructive effect" on the Rh-positive erythrocytes of the infant. Except for the existence of an apparent reciprocity of titer trends, no definite cause and effect relationship between the Rh agglutinin and the blocking antibody can be inferred from our data. In no instance did both the Rh agglutinin and the blocking antibody titers rise or fall simultaneously in a given patient.









CASE	OBSTETRICAL HISTORY	WEEKS ANTE-PARTUM						DE-LIVERY	CHILD	CLINICAL HISTORY	WEEKS POST-PARTUM	
		30	26	21	16	10	6				1	6
MF	GRAVIDA V PARATI I Spontaneous abortion 1937 II FTND 1939 Child is RH positive III FTND 1941 Child is reported RH positive Hemolytic disease of the newborn, survived with transfusions IV Spontaneous abortion 1943 V Present									AT BIRTH HGB 76% RBC 470 NRBC 5/100 WBC AET 3 DAYS HGB 105% AET 4 DAYS Slight jaundice Spleen and liver palpable HGB gradually dropping to lowest point at AET 2 WKS HGB 64% RBC 310 AET 5 WKS HGB 68% RBC 301 NRBC 14/100 WBC AET 6 WKS HGB 70% RBC 340		
								Spont				
MS	GRAVIDA VII PARATI I FTND 1933 II Cesarean, normal 1942 III Cesarean, died aet 3 days of atelectasis, jaundiced at time of death, but no autopsy performed 1944 IV } Early abortions V } VI } VII Present									1st DAY (am) HGB 104% RBC 424 NRBC 11/100 WBC (pm) HGB 111% RBC 476 NRBC 2/100 WBC AET 1 DAY HGB 100% RBC 443 NRBC 0 AET 5 DAYS HGB 88% RBC 389 AET 6 DAYS HGB 81% RBC 372 Transfused AET 7 DAYS HGB 112% RBC 524 NRBC 0		
								Cesarean				
JSm	GRAVIDA III PARATI I FTND 1935 II FTND 1941 III Present									AT BIRTH Cord blood: HGB 105% RBC 520 NRBC 59/100 WBC AET 1 DAY HGB 105% RBC 519 NRBC 1/100 WBC AET 5 DAYS Slight jaundice HGB 87% RBC 419		
								Induced				
JSn	GRAVIDA II PARAT I FTND 1943 II Present									AET 1 DAY HGB 77% RBC 410 NRBC 1/100 WBC AET 3 DAYS HGB 91% RBC 421		
								Induced				
LEGEND: ANTI-RH  BLOCKING ANTIBODY  CHILD  Subclinical hemolytic disease of the newborn Survived 												




Fig. 9.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are immediate. Part "B."

If the titer of one antibody rose as pregnancy progressed, the titer of the other either remained constant or dropped. Conversely, if the titer of one antibody dropped, the other was either maintained at a constant level or it rose in the last weeks of pregnancy; and if one antibody titer remained constant, the other rose, remained constant, or dropped. The reciprocity in the trends of antibody titers might be significant or insignificant depending upon the specificity of the present laboratory methods of testing for the antibodies. This is especially true of the blocking antibody test since it is a negative test and, as such, allows more chance for the occurrence of nonspecific reactions, despite the recently suggested changes in the technique of the test.<sup>24, 27</sup> As has been




of the infants, born to women who exhibited such antepartum trend of Rh-agglutinin titer, were capable of surviving. No inferences can be drawn from this observation, since so few of the infants in this group lived for more than a few hours after birth.

In summary, the women of Group I (who bore normal Rh-negative infants) show practically no Rh agglutinins or blocking antibodies in their sera at any time; those of Group II (who bore normal Rh-positive infants) show demonstrable antibodies only after parturition; those of Group III (who bore Rh-positive infants afflicted with subclinical hemolytic disease of the newborn) show significant rising titers of Rh agglutinin or blocking antibody beginning about ten weeks ante partum, reach a maximum level at the second postpartum week,

CASE	OBSTETRICAL HISTORY	WEEKS ANTE-PARTUM						DE-LIVERY	CHILD	CLINICAL HISTORY	WEEKS POST-PARTUM	
		30	26	21	16	11	6				6	10
GC	GRAVIDATI PARATI TCesarean died aet 39 hours TI Present	-	-	-	-	-	-	Cesarean		AT BIRTH Clinically normal HGB 93% RBC 4.76 NRBC 14/100WBC 1st DAY HGB 83% RBC 3.94 NRBC 0 Transfused AET 1 DAY HGB 107% RBC 5.68 AET 9 DAYS: HGB 104% RBC 5.57 Anemia	-	-
DS	GRAVIDATI PARATI TSillbirth at 7½ mo 1943 TI Present	-	-	-	-	-	-	Spont		AT BIRTH Brown-yellow amniotic fluid Yellow vernix Sluggish-respurred resuscitation HGB 86% RBC 4.4 NRBC 1/100WBC AET 1 DAY HGB 101% RBC 3.64 NRBC 1/100WBC AET 4 DAYS: HGB 106% RBC 4.74 NRBC 1/100WBC	-	-
EL	GRAVIDATI PARATI TSpontaneous abortion at 6 mo 1942 TI Present	-	-	-	-	-	-	Cesarean		AT BIRTH HGB 92% RBC 4.58 NRBC 5.5/100WBC AET 10 HRS HGB 8.4% Transfused with Rh-negative blood AET 1 DAY HGB 8.4% RBC 4.10 NRBC 1.5/100WBC AET 9 DAYS HGB 88% RBC 4.20	-	-

**LEGEND:**

ANTI-RH BLOCKING ANTIBODY




Subclinical hemolytic disease of the newborn-CHILD Survived 

Fig. 8.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are immediate. Part "A."

and then drop; and those of Group IV (who bore Rh-positive infants suffering from frank erythroblastosis fetalis) show high titers early in pregnancy which tend to drop gradually as pregnancy progresses. In Group IV the Rh-agglutinin titer tends to drop as the blocking antibody titer rises, and following delivery the Rh-agglutinin titer rises to a maximum peak at the second week post partum. Cases demonstrating a constant antibody titer throughout pregnancy and in the immediate puerperium cannot be readily distinguished from those exhibiting the "carry-over" phenomenon. The final differentiation between the latter is dependent upon a complete history of the cases in question.

In regard to the fetus, these data show that the more intense the antibody titers and the longer the time ante partum that they are demonstrable in the

only mildly afflicted with hemolytic disease of the newborn (all of whom survived), the average blocking antibody titer was higher in relation to the titer of Rh agglutinin than that found among the women of Group IV, whose infants were severely diseased (only three of twenty-one of whom were capable of surviving). Case V. M. (Group IV), whose twin babies were among the three in this group who did survive, demonstrated one of the highest titers of blocking antibody found in any of the cases studied. Also in the four cases mentioned above<sup>28</sup> where the maternal titers of Rh antibodies were very high and the Rh-positive infants escaped disease, the average titer of Rh agglutinins was lower than that found among the women of Group IV, while the average titer of blocking antibody was appreciably higher. All these findings seem to emphasize the protective rather than the destructive action of the blocking antibody on the erythrocytes of the fetus. Of the twenty women of Group IV tested for Rh agglutinin ante partum, six delivered stillborn infants, while the remaining fourteen bore infants who were alive at birth. Among the sixteen women who were tested ante partum for the presence of blocking antibody, four were delivered of stillborn infants. Since only one of the latter was tested for blocking antibody earlier than seven weeks ante partum, the following study was made on all patients for only the last seven weeks of pregnancy (Table V and Fig. 7). Both means of presenting these data, by case and by average trend of titer, show the same relationship—the women whose infants were stillborn had more Rh agglutinin and less blocking antibody in their sera than those whose infants were alive at birth. The same relationships appear to hold post partum. This again supports the idea that the presence of blocking antibody in the serum of a patient is not more serious than the presence of Rh agglutinin alone. With respect to the average findings in the cases included in this analysis, it might even be suggested that the observation of blocking antibody in the serum of a patient slightly increases her chance of being delivered of a viable infant, although Levine has stated that, "At any rate, it is certain that *in vivo* the specific reaction [the "specific union," which is the first phase in the Rh-agglutinin reaction and the only phase in the blocking antibody as measured *in vitro*] goes to completion so that the end result is hemolysis. In other words, clinically, one cannot differentiate erythroblastotic infants of mothers who have anti-Rh agglutinins from those whose mothers have the incomplete antibody."<sup>45</sup> The latter statement, however, does not coincide with the diagrammatic scheme suggested by Wiener<sup>14</sup> in which ag-

TABLE V. CASE DISTRIBUTION BY ANTEPARTUM RH-ANTIBODY TITERS OBSERVED IN WOMEN OF GROUP IV WHOSE INFANTS WERE STILLBORN AND IN WOMEN OF GROUP IV WHOSE INFANTS WERE ALIVE AT BIRTH

AMOUNT OF ANTIBODY DEMONSTRATED	MOTHERS OF STILLBORN INFANTS		MOTHERS OF LIVEBORN INFANTS	
	RH AGGLUTININ (6 CASES)	BLOCKING ANTIBODY (4 CASES)	RH AGGLUTININ (14 CASES)	BLOCKING ANTIBODY (12 CASES)
Low titer	1	2	5	4
Moderate titer	1	1	4	2
High titer	4	1	5	6

stated above, the blocking antibody does not seem capable of completely masking the Rh agglutinin, although it may partially obscure the intensity of the reaction in some cases. Conversely, the presence of the blocking antibody may be hidden by the Rh agglutinin (Case C. V.—see Fig. 5). Also, greater quantities of both antibodies may be present than can be detected in the laboratory, the unrecognized portions being involved in interaction with the erythrocytes of the fetus, and thus not be free in the maternal serum. At present there is no concrete evidence that the apparent reciprocity noted *in vitro* between these antibodies also occurs *in vivo*, although such a possibility might be assumed. An extreme instance of reciprocity is illustrated by case T. B. (Fig. 10)—such a marked interchange of antibody is uncommon, although milder reactions of this type have been observed several times in our laboratory. The fact that a

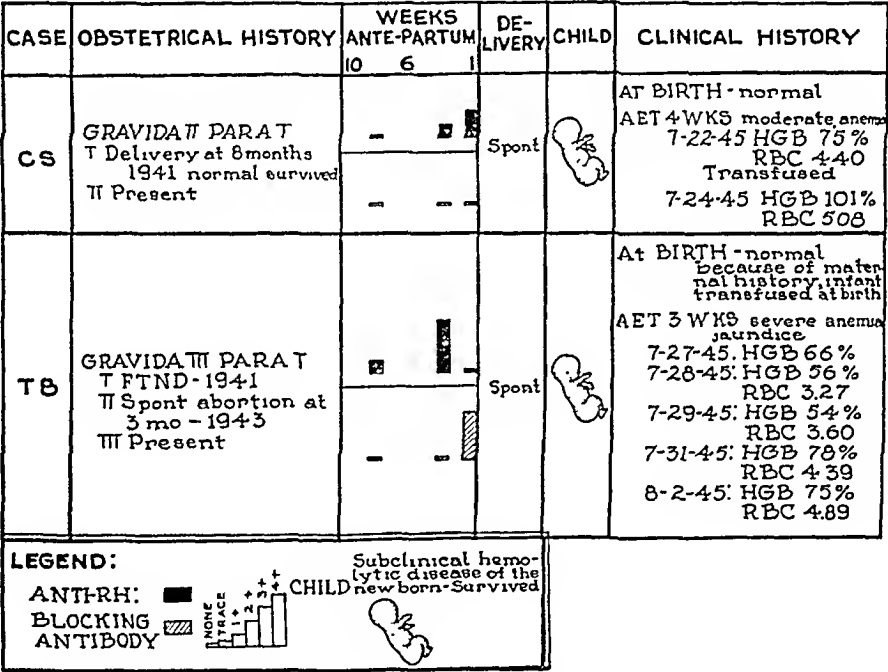


Fig. 10.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are delayed.

general reciprocity of titer trend is the only laboratory evidence of interrelationship suggests that the two types of antibodies are not merely two types of response to the same reaction, i.e., sensitization of the Rh-negative mother. It may well be that the relationship of the two antibodies is one of antagonism, and that when the strength of one rises that of the other must fall. Wiener wrote that "... the presence of Rh-blocking antibodies is of more serious prognostic import than the presence of Rh agglutinins without blocking antibodies; for example, when blocking antibodies are present, stillbirths are more likely to result,"<sup>13</sup> and also that "... the serums of mothers delivering stillborn erythroblastotic infants almost invariably, if not always, contain blocking antibodies, ..." <sup>15</sup> The observations made in this study do not support these statements. Among the women of Group III, whose infants were

glutination and subsequent hemolysis by the Rh agglutinin cannot occur if the blocking antibody has already reacted with the Rh agglutininogen.

With the few exceptions already noted, none of the women in this series who showed high antepartum titers of either antibody gave birth to clinically normal infants. No patient of Group IV (delivered of a severely diseased infant) demonstrated only the blocking antibody in her serum, while there were several in whose sera only the Rh agglutinin could be detected. This fact, supported by data previously discussed, suggests that the Rh agglutinin is developed first in the sera of Rh-negative women bearing Rh-positive infants, and that the blocking antibody appears later, *perhaps* as a specific protective response to the Rh-positive erythrocytes of a given phenotype of the infant. Thus, the patients in whom the Rh agglutinin only is demonstrable may be in a "less advanced stage of sensitization" than are those in whose sera the blocking antibody also is detected.

Several findings suggest the hypothesis that the blocking antibody may be produced, not as a defense for the mother, as is the Rh agglutinin, but as a protection for the erythrocytes of the fetus. The blocking antibody, as it is observed in the laboratory, might be a complete product in itself, independent of the Rh agglutinin, but it could also be a product resulting from the breakdown of the agglutinin by some intermediate substance whose production has been stimulated in an effort to protect the erythrocytes of the fetus. The diagrammatic scheme used by Wiener<sup>14</sup> to illustrate the Rh agglutinin and blocking antibody reactions may be modified to illustrate the latter possibility by assuming that the Rh agglutinin is cleaved by an unknown intermediate factor to produce two units of blocking antibody for each single unit of the agglutinin. This fanciful hypothesis is not inconsistent with the facts concerning the nature of the production of the blocking antibody as defined by other investigators.<sup>4, 46-48</sup> If the mechanism of cleavage of the Rh agglutinin actually occurs, the present laboratory test for the blocking antibody is even less adequate than previously considered, since only the product of the reaction, rather than the protective factor itself, is being measured. Although the role of the "blocking antibody" (the substance recognized in the laboratory as blocking antibody, or the protective factor discussed above) may be one of protection for the erythrocytes of the fetus, it may not always be able to carry out this function successfully because of the amount of Rh agglutinin already present and acting upon the Rh positive erythrocytes, or because of other as yet unidentified physical or biochemical factors.

In this study, two of the four women whose infants were stillborn (Group IV) showed no blocking antibody prior to delivery, and a third demonstrated a moderate titer of the antibody only in the last week before parturition. Case B. J. (probably demonstrating the "carry-over" phenomenon) was the only one of the four who showed a marked titer of this antibody throughout pregnancy. The titer in this case dropped late in pregnancy, at approximately the same time that the fetus died in utero. The sera of three of the twelve women whose infants were liveborn (Group IV) contained no demonstrable blocking antibody ante partum (Case M. Mc. was tested only once in the fifth

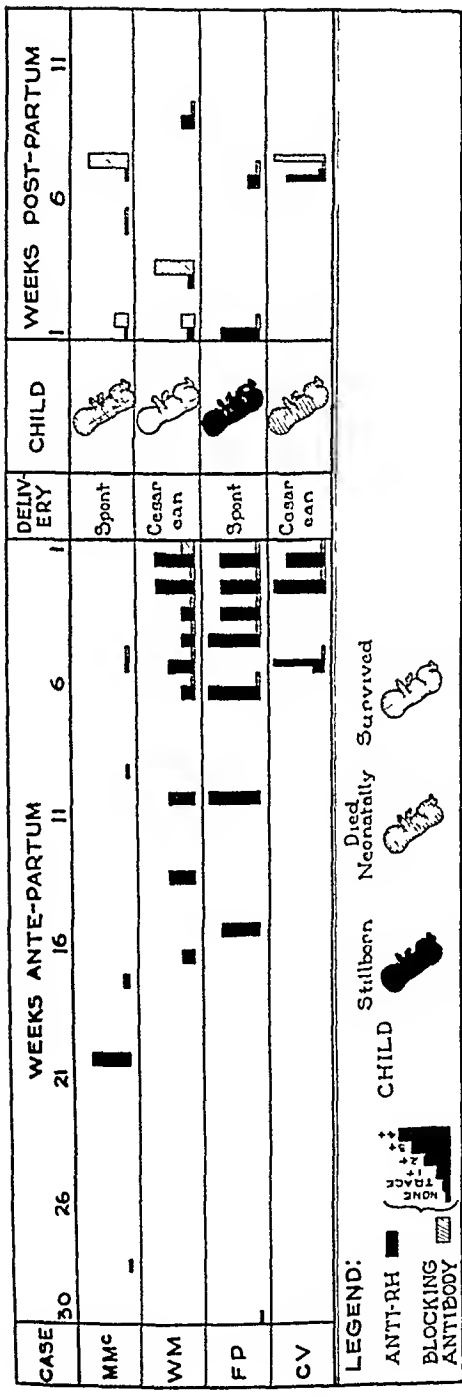


Fig. 11.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by amount of blocking antibody present ante partum). Part "A." Cases showing little or no blocking antibody ante partum.

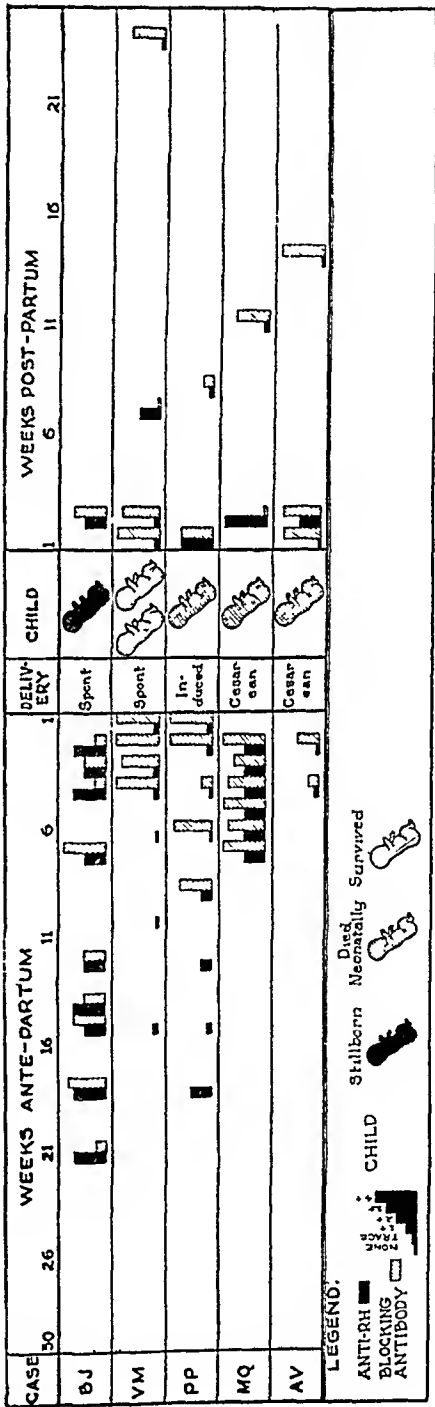


Fig. 12.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by amount of blocking antibody present ante partum). Part "B." Cases showing a high titer of blocking antibody ante partum.

cleavage of the Rh agglutinin. It usually appears late in the process of sensitization and its apparent function is to protect the fetal erythrocytes from destruction by the maternal Rh agglutinin. The probability of survival of Rh-positive infants born to Rh-negative women is better among those infants whose mothers demonstrate large amounts of blocking antibody in relation to Rh agglutinin.

### Summary

A detailed analysis is presented of both the individual and collective laboratory findings in 179 pregnant Rh-negative women. The study was undertaken in order to determine the relationships which might exist between the serologic data observed in the mothers and the clinical conditions found in the infants born to them, with the ultimate purpose of presenting the obstetrician with an antepartum interpretation of the significance of the laboratory findings in Rh-negative patients.

1. In order to facilitate the expression of the end results and significance of iso-immunization in pregnancy, the collective data were classified and studied according to the Rh characteristic and clinical outcome of the infant: Group I—normal Rh-negative infants; Group II—normal Rh-positive infants; Group III—Rh-positive infants with subclinical hemolytic disease of the newborn; and Group IV—Rh-positive infants with frank hemolytic disease of the newborn.

2. Of 61 Rh-negative women delivered of normal Rh-negative children, 9 showed isolated low titers of Rh agglutinins ante partum.

3. The isolated occurrence of Rh antibodies of low titer in Rh-negative women having Rh-positive husbands may be significant under circumstances where evidence of immunization occurs early in pregnancy or where blocking antibodies mask the Rh agglutinins. Apparently spurious positive tests for Rh antibodies may be due to the "carry-over" phenomenon or to pregnancy itself.

4. Antibody formation occurred more often among multiparous than among primiparous women. Nevertheless, it is important to test Rh-negative women repeatedly for Rh antibodies, regardless of parity. The ease with which some individuals may become immunized and the fact that an opportunity for previous immunization may have been forgotten influences the results of the tests in primiparous women.

5. Rh-antibody trends were determined for all women showing development of sensitization and their possible significance is shown in relation to the outcome of the child. In general, no patient demonstrating a high antepartum titer of either antibody, especially if their presence were detected early in pregnancy, was delivered of a clinically normal Rh-positive infant.

6. A comparison of the occurrence of Rh agglutinin and blocking antibodies indicates that no definite cause and effect relationship between them can be inferred from our data. There appears to be an apparent reciprocity between the titer trends of these two antibodies, the significance of which is not entirely clear. The Rh agglutinin appears to be demonstrable in the maternal serum by the twentieth week ante partum. The blocking antibody follows

antepartum week), and that of a fourth showed only a small amount in the last week before parturition. One of the three whose ante partum blocking antibody tests were negative (C. V.) apparently did have blocking antibody whose presence was masked by an Rh agglutinin of a different specificity. If it is considered that the presence of blocking antibody is a protection to the infant, and that a moderate amount appearing only in the last week before delivery cannot be effective in this role, then three of the four stillborn infants and three of the twelve liveborn infants lacked this form of protection. The difference of percentage incidence in the two groups (75 per cent as compared with 25 per cent) is twice its own standard deviation, thus strongly suggesting, although not definitely proving, a truly significant difference.

It has also been noted in this laboratory that a sensitized Rh-negative woman, previously delivered of a severely afflicted Rh-positive infant, may be subsequently delivered of Rh-positive infants who are only mildly affected with hemolytic disease of the newborn—in other words, that there is not necessarily a progression of severity of disease among the Rh-positive offspring of a sensitized Rh-negative woman. It is conceivable that in such cases, the Rh-positive erythrocytes of the infants (at least those of the less severely afflicted), are of an antigenic composition capable of stimulating the production of blocking antibody (as yet, only a blocking antibody of the specificity of anti-Rh, has been demonstrated<sup>21, 22</sup>) and are thus provided with a measure of protection against the previously formed agglutinin.

If these hypotheses as to the character and function of the blocking antibody are correct, then Group III in this analysis (Rh-negative women whose infants are only mildly affected with hemolytic disease of the newborn) may be composed of two types of cases. Some of the women probably do fall in the position intermediate to Group II (in which Rh antibodies are being developed by the Rh-negative mother but are not yet of sufficient strength to harm the Rh-positive fetus) and Group IV (in which Rh antibodies have been developed to such an extent that the Rh-positive fetus is severely afflicted). However, there are probably some women included in Group III who should really be classified in a Group V, their infants being only mildly affected by the maternal antibodies because of the overwhelming preponderance of blocking antibody in relation to subgroup specific Rh agglutinin. Certainly the obstetric histories of some of the women classified in Group III suggest that in their prior pregnancies they produced infants who were more severely afflicted than those born in their later pregnancies. As yet, the two types of cases cannot be definitely distinguished.\*

In summary, an apparent reciprocity exists between the Rh agglutinin and the blocking antibody, both in the single observations and in the trends of the titers. This may be due to inadequate laboratory methods, or to an antagonistic relationship between the two antibodies in vivo.

The blocking antibody as it is observed in the laboratory may be a complete product in itself (an anti-Rh agglutinin) or a product resulting from the

\*A partial explanation of this phenomenon might have been possible had we had the necessary subgroup sera which would have enabled us to determine the phenotypic characteristics of the blood of the infants born to these women.

## FALSE POSITIVE Rh TYPING OBTAINED WITH COMMERCIAL ANTI-Rh<sub>0</sub> SERUM

RICHARD D. PETTIT, M.D., AND EDWARD EVANS, M.D., PASADENA, CALIF.  
(From St. Luke Hospital)

IT IS not our purpose to add to the voluminous literature another case report of a transfusion reaction due to transfusion of an Rh sensitized individual with Rh-positive blood. There are, however, certain features of this case which will be of interest to the obstetrician and which will serve as a warning to those who rely upon the accuracy of Rh typing. The technical difficulties of Rh typing and the variation in the agglutinin titer of the various anti-Rh sera are well known to immunologists and hematologists working in this field, but are not so generally appreciated by the clinician and the medical technologist. False negative Rh typing has been reported many times, but false positive reactions such as this instance have not been reported to date. It is hoped that this case report will provoke some discussion as to the mechanism of the false positive Rh typing, and bring to light other such instances.

### Case Report

Mrs. D. G., aged 24 years, St. Luke Hospital, number E 1840, was admitted to the hospital on May 16, 1946. Her last menstrual period was Oct. 8, 1945, and the estimated date of confinement was July 15, 1946. She had felt no fetal movement since the first of May. A diagnosis of intrauterine death was made by her obstetrician, and labor was induced by artificial rupture of the bag of waters followed by administration of pituitrin. After thirty hours of labor she was delivered of a stillborn infant by low forceps. There was considerable bleeding, and a manual extraction of the placenta was necessary. The fetus was macerated and foul smelling.

Her postpartum course was moderately febrile. On the sixth postpartum day the red cell count was 3,160,000 and the hemoglobin was 9.3 Gm. She was typed and found to be Group A, Rh positive. An Rh-positive donor was cross matched, found compatible, and she was given a citrate transfusion. After 150 ml. of blood had been given she had a chill, and the transfusion was stopped. No gross hemoglobinuria or other untoward signs were observed.

On the seventh postpartum day, one of the authors (R.D.P.) was called in consultation. On examination, the uterus was tender and enlarged to the umbilicus. There was moderate vaginal bleeding. A curettage was done under sodium pentothal anesthesia with the removal of foul-smelling retained secundines. The uterus was lightly packed and penicillin was started. The pack was removed in eight hours; there was no further bleeding.

The patient was clinically improved, but it was felt that a transfusion was indicated. A second typing and cross matching was done under the consultant's supervision. She was again found to be Group A, Rh positive, and a donor of the same Landsteiner group and Rh type was cross matched. The slides were observed for one hour. There was no agglutination, and the blood was pronounced compatible. A citrate transfusion of 500 ml. was started. At the end of fifty-five minutes, after 400 ml. had run in, she became nauseated



the appearance of the Rh agglutinin and may not be present in demonstrable amounts earlier than about the tenth week ante partum.

7. The hypothesis is suggested that blocking antibody may be produced, not as a defense for the mother as is Rh agglutinin, but as a protection for the erythrocytes of the fetus.

The authors wish to thank Doctors Borson, Dallas, Koeniger, Morton, Musselman, Page, Smyth, Stephenson, and Traut for the privilege of using material from their records, and for the assistance and helpful suggestions which they so generously offered, and particularly to Doctor Herbert F. Traut, Professor of Obstetrics and Gynecology, and Doctor Francis Scott Smyth, Professor of Pediatrics, without whose help this work could not have been accomplished.

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### Comment

The important point to be stressed in this case is the persistent false positive Rh typing obtained using a commercial animal anti-Rh<sub>0</sub> serum strictly according to the technique outlined by the pharmaceutical house. It is difficult to believe that this is an isolated case when one considers the widespread use of this type of animal Rh typing serum. We wish to point out the possibility of false positives and to suggest extreme caution in accepting a positive Rh typing in the face of the slightest clinical suspicion of erythroblastosis or of history of transfusion reactions. In such cases, the Rh typing should be determined with human antiserum of known potency using washed cells. It is an interesting point to speculate if these false positives occur only in individuals already sensitized to one of the Rh antigens. Could the mechanism be a coating of the cells with a blocking antibody which in the presence of an agglutinin would cause the cells to agglutinate?

### Summary

The first case report known in which a persistent false positive Rh typing was obtained using a commercial animal anti-Rh<sub>0</sub> serum and unwashed cells is submitted.

The patient had been sensitized previously by a transfusion of Rh positive blood and by a pregnancy in which the fetus was probably erythroblastotic. The patient's blood was shown to contain significant titres of anti-Rh' agglutinins and anti-Rh<sub>0</sub> blocking antibodies.

The authors wish to express their thanks to Sister Mary Mark, laboratory director, St. Luke Hospital, for her stimulating interest and very considerable help in this case.

696 EAST COLORADO  
117 EAST GREEN

with emesis so the transfusion was stopped. Fifteen minutes later she had a severe chill accompanied by dyspnea and cyanosis. Just before this she had voided 700 ml. of clear urine, but the next urine specimen several hours later was grossly bloody and was only 50 ml. in amount.

She was immediately alkalinized by the intravenous administration of sodium citrate, sodium bicarbonate, and later, sodium lactate. The subsequent course was stormy, with the development of an oliguria in which the first 24 hour urine output was 120 ml., of severe generalized edema, of a rise in the nonprotein nitrogen to 97 mg. per 100 ml. of blood, and of a fall in the red cells to 2,850,000, with a hemoglobin of 7.5 Gm. Her condition was critical until the fourth day when slight clinical improvement was first noted. This was followed in twenty-four hours by an increased urinary output and, four days later, by a diuresis. The nonprotein nitrogen did not reach normal until three weeks later.

The patient had been retyped and recrossmatched immediately after the transfusion. The same results were obtained, that is: Group A, Rh positive.

Review of the past history revealed the following pertinent information: Four years previously she delivered a normal female infant after an uneventful pregnancy. She had a postpartum hemorrhage and was given a transfusion with her father as donor. There was no reaction.

Since the available clinical data indicated that the intrauterine death of the second infant was due to erythroblastosis fetalis and the transfusion reactions due to Rh incompatibility, the question of a false positive Rh typing was raised.

She was retyped using a commercial anti-Rh<sub>0</sub> human serum (Hyland) instead of the anti-Rh<sub>0</sub> animal serum (Lederle) previously used. With the human serum she was found to be Rh negative. The chief difference in the techniques employed with the two sera was that the cells were washed in the case of the human antiserum, whereas, in the case of the animal antiserum, unwashed cells were specifically directed to be used. Using the technique as outlined by the circular accompanying the animal serum, the typing was always Rh positive, but, if the cells were washed, the typing was Rh negative.

The patient, her husband, her father, and her child were typed by Dr. Roy Fisk, immunologist to the Huntington Memorial Hospital, Pasadena, California, using human anti-Rh serum. He found the following: The patient and her child were Rh negative. The patient's father and her husband were Rh positive. The patient's serum contained anti-Rh agglutinins.

As a further check, blood was sent to Dr. Alexander Wiener for typing and Rh antibody titration. The following are his results:

Mother	A <sub>2</sub>	MN	Rh negative
Child	A <sub>2</sub>	M	Rh negative

Agglutinin test:

Rh<sub>1</sub> cells—positive up to dilution 1:8  
Rh<sub>2</sub> and rh cells—negative

Conglutination test:

Rh<sub>1</sub> and Rh<sub>2</sub> cells—positive up to 1:1000  
rh—negative

Blocking test:

Rh<sub>1</sub> and Rh<sub>2</sub> cells—positive reactions  
blocked up to serum dilution 1:1000

Interpretation:

Patient's serum contains a mixture of antibodies—anti-Rh<sub>0</sub>'. This consists of a weak anti-Rh' agglutinin (titre 1:8) and a strong anti-Rh<sub>0</sub> blocking antibody (glutinin) of titre 1:1000.

TABLE I. NUTRITION AVAILABLE FOR PREGNANT WOMEN (THE HAGUE AND LEIDEN)\*  
From evaluation by H. M. Sinclair, Oxford Nutrition Survey, for S.H.A.E.F.<sup>15</sup>

ITEM	RECOMMENDED DAILY ALLOWANCE†	SEPTEMBER '44	FEBRUARY '45	APRIL '45
Calories	(2,500)	1,925	731	912
g. Protein (vegetable)	(85)	38	24	28
(animal)		23	9	11
g. Fat		50	11	14
mg. Calcium	(1,500)	1,075	649	517
mg. Iron	(15)	16.3	9.6	10.7
I.U. Vitamin A	(6,000)	1,260	445	766
mg. Thiamin	(1.8)	1.1	1	0.6
mg. Niacin	(18)	9.2	3.0	4.1
mg. Riboflavin	(2.5)	1.2	0.5	0.5
mg. Ascorbic acid	(100)	59	34	53

\*Reasonably similar in Rotterdam.

†Food and Nutrition Board, 1945.

gether in most of this presentation. Numerous less formal investigations and interviews were made to check specific points.\*

Upon pregnancy in general, an outstanding effect of hunger was a fall to one-third of the expected number of births representing conceptions during the undernutrition period. This period was marked by amenorrhea in about 50 per cent of women, with normal menstruation reported only in about 30 per cent.<sup>16-18</sup> The nutritional basis of "war amenorrhea" has been investigated by others,<sup>19-21</sup> and in Sydenham's recent study<sup>21</sup> seems suggestively connected with insufficient protein intake. Menstruation in the Dutch women, as in those of other studies mentioned, was regularly resumed with the return of food. The gross interference with this function, with its striking result upon later birth rate, testifies to the stringency of nutritional conditions during the hunger winter. All of the pregnancies whose records were used in this study were analyzed to determine whether maternal age or parity were altered from the normal. No significant change occurred in these underlying factors. Therefore, though fewer women conceived during the months of undernutrition, those who did so, or who gave birth, at that time were not essentially different from the patients of pre-hunger or post-hunger times who served as controls.

As a pediatrician, the author can only record his findings and those of Dutch obstetricians in general upon toxemia of pregnancy with a minimum of speculation. Although a number of German authors reported a decrease in toxemia during starvation in the former war,<sup>22</sup> the nutritional significance of their conclusions has been criticized.<sup>23</sup> More recently, the general consensus has been that a definite reciprocal relation exists between nutrition—especially

\*The physicians and others in The Netherlands who gave assistance were too numerous for acknowledgment of thanks individually. Professors A. Holmer and E. Gorter of Leiden, K. de Snoo of Utrecht, M. v. Boudijk Bastlaanse, S. van Creveld and B. C. P. Jansen of Amsterdam, were sources of especial knowledge and assistance. To Dr. A. van Ormondt of Amsterdam and Dr. J. H. P. Jonxis of Rotterdam the author is grateful for aid in innumerable matters. Dr. C. Banning, Dr. den Hartog, and Dr. Dols of The Hague supplied highly useful official statistics. Miss D. Ten Haaf, the President of the Dutch Dietetic Association was constantly helpful, as were the many services provided by the American Red Cross in The Hague. Dr. J. Rietdijk, Miss Rijkenberg, and Dr. R. F. van Wering placed the records and hospitality of the Midwifery School entirely at our disposal, as did the administration of the Zuilwyl Hospital. Records were painstakingly transcribed by Miss Dini Kersteman, Miss M. Brandenburg, Drs. H. F. Bekemann, and H. C. Rietdijk.

## THE EFFECT OF WARTIME STARVATION IN HOLLAND UPON PREGNANCY AND ITS PRODUCT\*†

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THE association of maternal malnutrition with improper growth or development of the fetus, prematurity, stillbirth, and neonatal death, and with toxemia during pregnancy, has been strongly indicated by numerous researches.<sup>1-13</sup> Nevertheless, proof is needed that this relationship is actually one of cause and effect. Unsatisfactory pregnancies may, of course, occur in ill-nourished women merely because women of suboptimal health and hygiene tend to eat improper diets.<sup>12</sup> Test circumstances in which maternal diet is the only variable are obviously needed. The mass malnutrition in western Holland during the "hunger winter" of 1944-45 seemed likely to offer useful data of this type. Results of a study made in Rotterdam and The Hague are presented elsewhere insofar as their effects upon the newborn infant are concerned.<sup>14</sup> The present paper amplifies certain of those data and describes the effects upon the mother during pregnancy as well.

The causes and other details of the Dutch starvation period need not be discussed here, so that space will be given only to a brief account of the type and duration of nutritional inadequacy. The food situation began to deteriorate in October, 1944, and in December reached a low level rather steadily maintained until liberation of the country in May, 1945. Therefore, the critical period lasted at least five months, but not more than eight. Thus, pregnancies ending just before relief of hunger had begun in relatively good nutritional circumstances; on the other hand, those beginning during hunger were ended after relief. The data of Table I show probably the most reliable estimate of food available to pregnant women in representative months of the hunger period.<sup>15</sup> It is noteworthy that what occurred was a relatively brief period of severe, generalized undernutrition, not outstandingly poor for any single dietary element. The main sources of data used for analysis of the results upon pregnancy were the records of the National School for Midwives at Rotterdam, and the Obstetrical Service of the Zuidwal Hospital at The Hague. Since the major findings from both institutions showed parallel trends, they will be grouped to-

\*Presented, by invitation, at the meeting of The American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

†The studies being reported, as well as the author's trip to Holland, were a part of a continuing research project, financed by the Nutrition Foundation, New York City, and conducted by the Department of Maternal and Child Health, Harvard School of Public Health, at the Boston Lying-in Hospital, in collaboration with the Department of Obstetrics, Harvard Medical School.

winter. The decline in birth weight which followed was steeper among the constitutionally larger infants (upper percentiles) than among the smaller ones, a fact equally notable in the rise after liberation and return of food. From the 50 percentile or median line, which is of most significance statistically, it appears that babies born just before return of food weighed scarcely less than those born two to three months earlier. Since the undernutrition of mothers giving birth just before the Liberation must have begun much earlier in pregnancy, it is apparent that birth weight reflects the nutrition of late pregnancy rather than that earlier in gestation. Finally, it must be stressed that individual pregnancies showed exceptions to these findings. Only in the analysis of fairly large groups does the fundamental relation between maternal nutrition and fetal weight gain clearly appear.

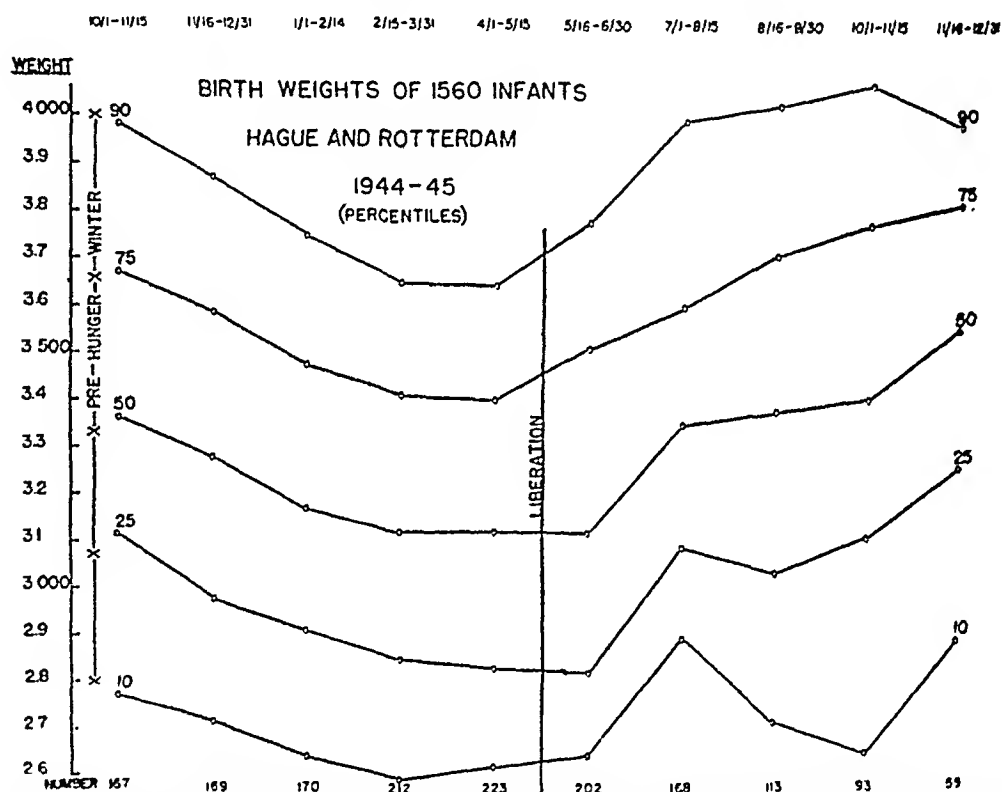


Fig. 1.—Change in distribution of birth weights for infants born in ten successive periods of one and one-half months each, Oct. 1, 1944, to Dec. 31, 1945. Lines connect the same percentile for each period.

The 50 percentile represents the median, as half the infants are above that weight and half below; 10 per cent are below the 10 percentile, and 10 per cent above the 90 percentile. Crosses at left indicate the same percentiles for infants born during the previous winter.

Although accurate figures as to birth length are not so easy to obtain, those from the two clinics (Fig. 2) showed a relatively greater number of short babies during the months of hunger than before or thereafter. As hunger progressed the changes did not follow the same smooth curve from period to period as did those for weight. Nevertheless, the total group of infants born under hunger circumstances were shorter by a statistically significant degree than the total group born previously, or born after the return of food. Since length is only

TABLE II. UNDERNUTRITION AND TOXEMIA  
(Midwifery School, Rotterdam)

PERIOD	PRE-WAR (1938-9)	IMMEDI- ATELY PRE-HUNGER 1944	HUNGER (1944-5)	IMMEDI- ATELY POST-HUNGER (1945)
Number of patients at risk (5-9 months pregnant)	3,360	975	2,254	875
A.—Per cent diagnosed toxemia (un-qualified)	3.2	3.4	1.9	3.8
B.—Per cent diagnosed toxemia, with B.P. at least 140, or albumin at least ++, or edema at least ++, or convulsions	2.2	2.4	1.1	2.2
C.—Per cent diagnosed toxemia, with albumin at least ++, or edema at least ++, or convulsions	0.8	0.75	0.6	1.7

protein nutrition—and frequency of toxemic states.<sup>4, 10, 24, 25</sup> It was therefore distinctly surprising to learn that all Dutch obstetricians had seen less than the expected amount of toxemia during the hunger period. Review of records from the Midwifery School substantiated this impression. Results are given briefly in Table II, in the preparation of which three diagnostic criteria were used. The first, (A) includes every diagnosis of toxemia of whatever degree. To restrict the diagnosis to a more definite one, cases were excluded unless they showed a blood pressure rise to 140 mm. or more, albuminuria or edema of at least grade 2 plus, or convulsions. This resulted in the second line of figures (B) in the table. Finally, the criterion of blood pressure was removed altogether because of the prevailing hypotension due to undernutrition,<sup>26</sup> and either marked albuminuria or edema, or convulsions, were required for the case to be included in the figures of line C. It will be noted that by none of these manipulations could the data be made to show any increase of toxemia during the undernutrition period. For two of the categories used in the table (A and B) a statistically significant\* decline in this condition appears to have occurred.

Though decline in toxemia was not assignable to any change in maternal age or parity, a factor difficult to evaluate was the definite scarcity in table salt available during the hunger period. The concurrent reduction of toxemia suggests that future studies of nutrition and toxemia must be carefully evaluated with regard to salt intake as well as to specific type and duration of maternal food habits. To say that a "good" diet will reduce the incidence of toxemia and a "poor" one increase it is futile until one can specify the exact elements constituting goodness and poorness in this regard.

Effects of maternal nutrition upon the birth weight of infants born in Rotterdam and at The Hague are shown in Fig. 1. Representation by percentiles (explained in the legend) shows that at the beginning of the critical period birth weights were distributed over about the same range as in the previous

\*The author is grateful to Miss Jane Worcester of the Harvard School of Public Health for evaluation of statistical data.

TABLE III. RESULTS OF PREGNANCY  
(Rotterdam and The Hague)

PERIOD → BORN DURING →		PRE-WAR '38-'9	PRE-HUNGER 10/1/43- 5/1/44*	HUNGER 12/1/44- 5/15/45	CONCEIVED IN HUNGER 10/1- 12/31/45
Births	Rotterdam	674	659	412	135
	Hague	—	171	342	47
	Total	674	830	754	182
Per cent abortion and miscarriage	Rotterdam	1.67	5.6	2.2	8.33
Per cent prematurity— less than 2,250 Gm.	Rotterdam	5.27	4.98	6.3	8.4
	Hague	—	8.2	6.4	11.0
	Total	5.27	5.7	6.3	9.1
Per cent stillbirth	Rotterdam	3.5	3.2	1.8	4.03
	Hague	—	2.9	0.3	4.25
	Total	3.5	3.16	1.0	4.1
Per cent neonatal death	Rotterdam	1.55	3.0	2.36	5.05
	Hague	—	6.1	1.77	4.65
	Total	1.55	3.66	2.05	4.94
Per cent malformed	Rotterdam	1.36	1.6	0.5	2.42
	Hague	—	0	1.82	4.44
	Total	1.36	1.26	0.97	2.95

\*11/1/43-4/1/44 for The Hague.

both clinics, the largest incidences occur in the post-hunger months, whose total case material is dangerously small for statistical purposes. Certainly during circumstances of marked nutritional inadequacy, no significant increase in premature births was recorded.

It was possible to confirm data for stillbirth by consulting municipal records from the cities of Rotterdam and The Hague as a whole. These were in agreement with Table III in showing no increase in incidence of stillbirth during the hunger winter. The tendency to increase in post-hunger months is probably related to the concurrent rise in percentage of premature births. Neonatal death occurred actually less commonly in the hunger period than before or after. Although the municipal statistics on this point were in disagreement with the hospital data, the former were largely based upon infants born at home and thus subject to all sorts of unusual privations. The hospital figures are more useful for our purposes.

Data as to congenital malformations do show a slight increase in the last column, but unfortunately the small number of properly timed pregnancies renders the difference of no statistical significance. Further investigations<sup>14</sup> also resulted unsatisfactorily in failing to define a relationship between maternal nutrition and malformations, largely because of low fertility at the critical period of nutritional stringency.

Lactation, judged solely by the percentage of mothers nursing their babies during the hunger period, was singularly unaffected.<sup>14</sup> There was no means of knowing the cost in maternal tissue involved, but the evidence indicated that a woman not receiving adequate food could still secrete milk enough to sustain a desperately hungry baby.



one dimension while weight is the product of three, changes in the former cannot be expected to be as sharp as those in the latter.

Statistics upon various undesirable outcomes of pregnancy are presented in Table III under four groupings according to maternal circumstances. The 674 pre-war pregnancies of 1938-39 (from the Rotterdam source only) represent a normal control period uninfluenced by war or malnutrition. The 830 pre-hunger deliveries from both clinics portray the fourth winter of Nazi occupation but a year before the hunger winter, whose figures are given by the third column. Finally, the last column was added to include infants born several months after the return of food, but conceived at the worst phase of starvation. The small number of births in this last group testifies to reduced fertility during the hunger period.

## ROTTERDAM AND THE HAGUE

## 1533 INFANTS

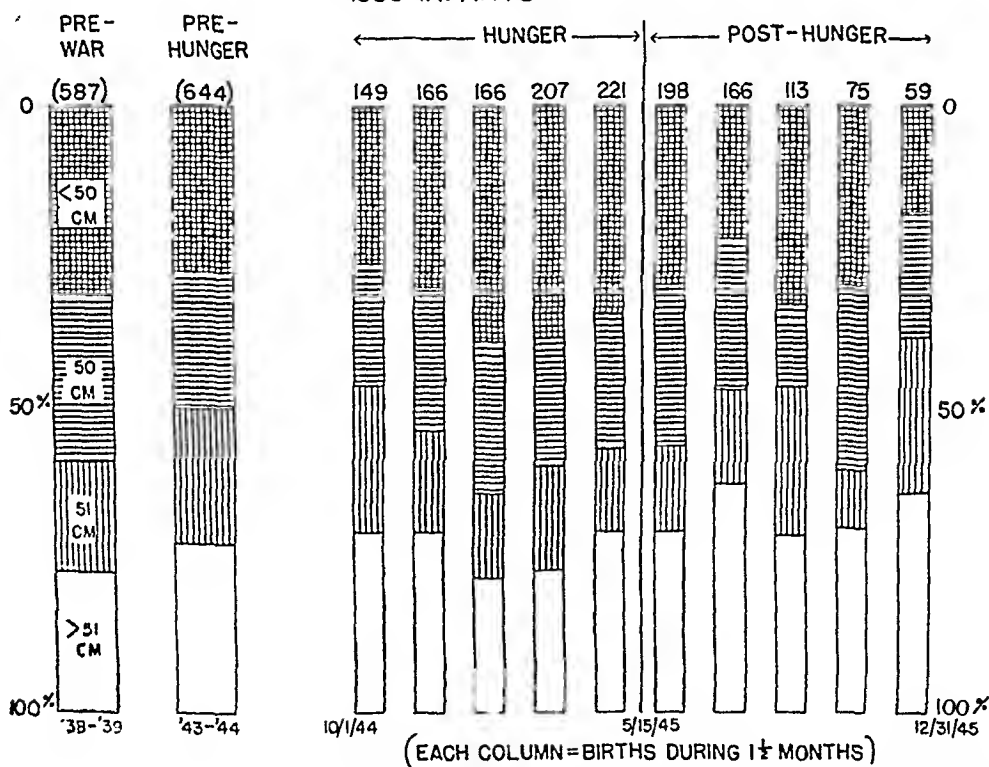


Fig. 2.—Percentages of infants in four ranges of birth length, before, during, and after hunger. The ten narrower columns represent the same ten successive periods used in Fig. 1. Number of infants measured given at top of each column.

Figures for abortion and miscarriage are included to satisfy the reader's curiosity, but there is no reason to assume that they are accurate or that conclusions can be drawn from them. Only the data from the Rotterdam clinic have been listed, as those from The Hague were even less serviceable. Prematurity, which was much more reliably recorded, was based in this analysis upon a weight criterion only, all infants of less than 2,250 Gm. (5 lb.) being so diagnosed. The slight increase in prematurity in the Rotterdam clinic during hunger was practically nullified by the actual decrease shown in data from The Hague. For

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## Discussion

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—Dr. Smith has emphasized in his paper that these nutritional deficiencies were of an acute nature and of relatively short duration. His charts indicate that the deficiency was quantitative rather than qualitative. The ratio of protein, fat, and carbohydrate, even at the worst period, was still approximately that recommended by the League of Nations Committee. In fact, the actual protein intake was no lower than that found by Dr. W. T. Tompkins in a Philadelphia survey of clinical patients five years ago. It is not particularly surprising, therefore, to find that there was no striking increase in the rate of prematurity and an actual decrease in the incidence of toxemia. As is well known overeating and rapid increase in weight are definitely associated with the toxemia of pregnancy.

An additional possible explanation of the decreased incidence of toxemia is the fact that a relatively large number of babies during this period were probably borne by multiparas, the younger persons being in military service or in impressed labor in Germany.

I would like to ask the author three questions:

1. Did these women show clinical evidence of nutritional or vitamin deficiency?
2. Are data available on anemia of these mothers?
3. What was the average gain in weight during pregnancy?

DR. PHILIP F. WILLIAMS, Philadelphia, Pa.—It is fortunate that Dr. Smith seized the opportunity to record studies of such a unique situation. We hope that starvation in such extreme degree may not occur again, and yet one hesitates to say it will not in the face of reports in regard to the food situation in many parts of the world today.

Toward the end of the first World War, two articles appeared on the effects of undernourishment, one in England and one in Germany. In England C. F. H. Smith reported on the effects of poor diets in London during the years 1915 and 1916. There were some differences in his findings and those of the speaker. Smith of London reported in that year a decrease in weight and in length of those children, a marked increase in toxemia of pregnancy, and, most surprising, an outstanding increase in the number of stillbirths, whereas

### General Comment and Summary

The severe undernutrition of the winter of 1944-45 in Northwestern Holland was marked by the following effects upon pregnancy and the fetus: (1) amenorrhea and infertility were so common as to reduce strikingly the expected number of births; (2) infants conceived before the hunger months but born during them were significantly below the expected weight and length. Evidence suggests the correlation of this effect with maternal nutrition during the last half or last trimester of pregnancy. (3) Toxemia was not increased, and by certain criteria was actually reduced in comparison with expected frequency; (4) prematurity and congenital malformations were slightly but not significantly increased in occurrence; (5) no effect was noted upon the incidence of still-birth, neonatal death, or lactation, when the latter is limited solely to the secretion of sufficient milk to support an infant.

These findings are surprising in view of the numerous recent studies suggesting a significant and clear-cut relation between maternal nutrition and almost all aspects of the course and product of pregnancy.<sup>1-3</sup> Of the various interpretations which suggest themselves, the first is that reports from Dutch cities were false, and that there was no lack of adequate food for pregnant women. This is certainly not true. The manifest decrease in birth weight during the hunger period should dispose of any doubts on that point.

A second interpretation is that these data from Holland are of real significance, whereas investigators working elsewhere<sup>4-10, 24, 25</sup> have mistaken association for etiology. This is considered to be unlikely, particularly in view of reports in which improvement in the course and product of pregnancy appears to have coincided with directed improvement of nutrition in a controlled group of patients.<sup>7-10</sup> The difficulty of proving that untoward results of pregnancy in ill-nourished women are the direct consequences of their nutritional status is, however, a real and challenging one.

A third interpretation, believed to be nearer the truth, is that the nutritional circumstances of the Dutch situation were not comparable to those of other studies in American, Canadian, and British obstetric clinics.<sup>4-10, 24, 25</sup> The Dutch women had been reasonably well fed until subjected to a brief period of acute general undernutrition. By contrast, the other studies usually involve women who have nourished themselves, more or less indefinitely as a rule, upon diets adequate in calories but insufficient in certain individual food elements. Quite possibly acute undernutrition may result in one way while chronic malnutrition may result in another. The need for careful analysis of the time factor in nutritional studies of pregnancy is strongly suggested. It is also obvious that fetal growth may be related to maternal caloric intake of late pregnancy, whereas fetal development and viability may rest, nutritionally speaking, as much upon the maternal circumstances before conception as upon those of pregnancy itself.

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DR. SMITH (Closing).—The points that were made will be taken up as briefly as possible. It should be stressed that all the data are not yet in my hands, and therefore everything has not been finally summarized. Therefore I cannot tell you at this time whether a substantial shift occurred in the ages of the mothers. As to the distribution of primiparas and multiparas, there has not appeared to be any change in the average parity before, during, or after the hunger. As my Dutch informants recalled the clinical picture, there were few evidences of specific nutritional deficiencies among these women. A great many trained nutritionists from England and from this country—somewhat to their disappointment—did not find numerous signs and symptoms of this sort when they went into starvation areas in Europe immediately after their liberation. I do have the records of maternal hemoglobins, but they are not yet tabulated.

I have begun an attempt to correlate maternal weight changes with the size of the infant. This is not easy because of the varied periods of pregnancy during which women gained or lost. Since a woman might gain in the sixth or seventh month and then lose in the eighth and ninth, or vice versa, one does not quite know where to begin in making tables. Certainly by the end of the hunger period the average woman had not gained more than 2 kilos (about 4 pounds) during pregnancy, and a large number had lost weight. It should be stressed that one saw small babies born to women who gained fairly well, and some women who failed to gain at all in the last three months had infants above average in size, but that there was a general falling off in birth weight is not to be doubted.

I do not like to discuss toxemia, but I like to be where toxemia is being discussed. The whole subject is highly controversial. Dr. DeSnoo seemed to feel, with his obstetric colleagues, that toxemia had definitely decreased. Most of them felt that the decrease in protein had something to do with it. Of course, women adequately nourished before the acute hunger period could have lived on their own tissue stores of protein. The important thing in the whole toxemia question seems to me the avoidance of sweeping statements on the basis of present knowledge.

We could evaluate the stillbirths accurately, from a large amount of data from the major cities as a whole, reliably reported. They did not decrease.

As to the accuracy of the data as a whole, one must sacrifice some of that in a mass study of this sort. The studies by trained nutritionists who very carefully analyze the diets of a comparatively few pregnant women continue to be most important. These provide accuracy but sacrifice large numbers. Apparently one cannot have both.

Lactation has of course been investigated by dairymen, whose interest is not so much in whether a cow can keep her calf alive as in whether she can produce a commercially valuable quantity of milk. I am sure that an improperly fed cow might support a calf but would not be a good producer of milk by other standards, and might lose a good deal of her own weight in the process.

the speaker reported a decrease in stillbirths which he could not evaluate. Mayer reported in Germany two significant things, the size and weight of the children, and the marked diminution in pregnancy. He states in that article that the weight of the children was not reduced to a marked degree, and he felt that it was appreciably reduced and could be attributed to the parasitic action on the part of the fetus.

I was interested in Dr. DeSnoo's remarks at a previous meeting that there had been a marked reduction in toxemia in his clinic patients in Utrecht when the food intakes were restricted. The diet of his patients contained an unusual amount of sodium chloride. Possibly his theory about salt restriction may have some part in the Rotterdam series reported this evening.

I think the extremely low amount of animal protein is significant. The diets must have contained a small amount of amino acids, and I was surprised that there were so few fetal malformations, with this low amino acid intake.

I was particularly interested in his remark that when the food intake was increased in the last trimester of these women who had had an extreme starvation diet the fetuses reached nearly normal weight at term, and wondered whether the increase in weight up to normal in those children was due to the food intake of the mother or to a remarkable recuperability of the fetus. I think it is true that the diet of the last trimester has much to do with the growth of the child. Of course, it is the period of greatest development, but I think these findings may to some degree modify our instructions to women as to diet in the various trimesters of pregnancy. Evidently, from his remarks this evening, Dr. Smith feels that the last trimester is the time when the greatest changes may occur in the fetus of a starved woman who has then been given a sufficient amount of food.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—Dr. Smith should tell us how accurate he thinks his figures are and should also interpret them. I am certain that when this paper is published, we will again have numerous reports on curtailing the size of the baby and on lowering the incidence of toxemia by diet restriction. Figures from Margaret Hague, from the New York Lying-In, and from the Chicago Lying-in hospitals would seem to indicate that the incidence of toxemia decreased during the war period. However, these figures are not correct, because some of these patients are now returning and we find that they did have mild toxemia which was not diagnosed for the pregnancies during the war period. The Chicago Lying-in hospital had a 40 per cent increase in the number of deliveries, a 60 per cent decrease in staff, and within one year a complete replacement of the house staff with inexperienced doctors. This accounts for the inaccuracy in the records and, in all probability, similar conditions occurred in other hospitals.

The statistics reported by the essayist in a country just ravaged by war must be used with caution.

MR. LOUIS CARNAC RIVETT, London, England.—I think the main point about this low diet is the length of its duration. In 1926, in my country, we had a rail strike, the result of which was that the entire population of several large areas remained out of work until this war started. I came into contact with a charitable person that was endeavoring to relieve the awful conditions in what we called "distressed areas," in South Wales and Northumberland, particularly in regard to expectant mothers. I think the time element was rather striking, and may account for some of the differences in what occurred in this rather short period in Holland, because I did not come into contact with the situation until this starvation diet had been going for four or five years.

The incidence of stillbirths and of puerperal sepsis was enormous. In one area 9 per cent of delivered mothers died of puerperal sepsis, and I am sure it was due to the chronic starvation. In a shorter period the body has a store that it draws on, particularly of the vitamins, which are perhaps more important than the amounts of nutrition over a short period.

any friable lesion, whether cancerous or, as we have recently found, pre-cancerous, will readily give off large numbers of its surface cells when this technique is used. The method offers excellent "surface biopsy" information regarding growth activity.

Certain evidence has been presented to show that small localized cancer lesions may not be visible to the naked eye. This has been a weak point in our method of doing a surgical biopsy, as the entire success of the biopsy procedure was dependent upon the lesion being visually demonstrable. We have recently encountered numerous cases where a single biopsy missed the growth while repeat sections revealed a small cancer.<sup>6</sup> On numerous occasions patients complaining of intermenstrual or postcoital spotting of blood have revealed a cervix which appeared normal except for a circular red area about the external os. In such cases it is sometimes difficult to know where to take the biopsy. The spatula method shows a distinct advantage in these cases, as the entire circle of the squamocolumnar junction may be "surface biopsied" simply by rotation of the spatula while gently pressed against the cervical os.

The spatula method has been found useful not only in cervical cancer, in which it offers its greatest contribution, but also in any surface cancer, e.g., tongue, lip, throat, skin, and vulva. Cytological diagnosis of other organs, e.g., stomach, lung, prostate, kidney, and bladder, must depend upon other cytology techniques which have been recently developed.<sup>7</sup>

The selective cytology technique has proved useful in the more accurate assay of endogenous estrogen by cornification counts from selected areas of the squamous tissue of the vagina and cervix in cases of cervical carcinoma. In the ordinary vaginal or cervical smear the profuse purulent and sanguineous discharge associated with the malignant disease frequently obscures the true (estrogenic) cornification level associated with malignant disease. The significance of this lies in the fact that abnormal endogenous estrogen levels have been found in association with cervical carcinoma<sup>8</sup> and precancer.

### **Spatula Technique for Selective Cytology Smear**

The method of taking the cervical smear for selective cytology requires first the adequate exposure of the cervix with a bivalve speculum. The mucus present at the external os is aspirated using a small glass pipette, or it may be wiped off with a cotton swab and discarded. (In many cases we take both the external os smear by aspiration and the spatula smear for selectivity. In these cases the aspirated mucus is placed on a slide for the usual staining procedure, preceding the taking of the spatula test.) Following the removal of excess mucus, the squamocolumnar junction is visualized. The precise method of taking the spatula test will vary according to the type of cervix, e.g., the presence of extensive lacerations or erosions will modify the procedure.

A nulliparous or healthy-appearing cervix showing the squamocolumnar junction just outside the circle of the cervical opening may readily be approached by simply placing the hook end of the spatula (Fig. 1, *a*) gently against the cervical opening. While held in this position a rotary movement permits light scraping of the entire squamocolumnar junction throughout its circumference (Fig. 2). The cellular material thus obtained in the surface mucus is then transferred to glass slides in the usual manner.

## SELECTIVE CYTOLOGY SMEAR FOR DIAGNOSIS OF CANCER\*

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THE diagnosis of malignancy by "cytology smears" of exfoliated cells has been gaining wide acceptance, as the reliability of this method has proved itself by actual practice. The original technique for the diagnosis of uterine cancer by the vaginal smear method was described in an epic monograph by Papanicolaou and Traut<sup>1</sup> in 1943. The principle of this technique was that the aspiration of the vaginal secretions contained an admixture of normal cells, mucus, leucocytes, and blood, but also specifically malignant cells exfoliated from any growth which might be present in the genital tract. The method has proved its reliability in the diagnosis of cancer as reported by numerous investigators (Meigs,<sup>2</sup> Ayre,<sup>3</sup> Jones,<sup>4</sup> etc.). It has been admitted, however, that the method was arduous and time-consuming in the microscopic search for the specifically malignant cells sometimes obscured by the cellular desquamata, leucocytes, and blood. Since then efforts have been made to improve the technique and simplify the method. In 1944, our first modification was the description of the external os cervical smear described in "A Simple Office Test for Uterine Cancer Diagnosis."<sup>5</sup> This method permitted a greater degree of speed and accuracy in the interpretation as, whether the lesion were fundal or cervical, a greater concentration of malignant cells was constantly found at the cervical os. More recently, we have searched for a method to detect evidence of the earliest cell change in malignancy and of precancerous cell changes.

It has long been known that the squamocolumnar junction of the cervix is the site of predilection for carcinoma of the cervix. At this key point, cancer is known to develop more commonly than from any other single focus. In an effort to study early malignant changes in the squamous cells thrown off specifically from this focus, the "spatula cytology technique" was developed in our laboratory. Previous cytology smear techniques consisted of the aspiration of cells which had already been exfoliated. The spatula technique is a means of collecting the cells before their exfoliation. This is performed simply by utilizing a small spatula to scrape gently the surface of the tissues at the precise squamocolumnar junction. The cells and secretions are then transferred to a glass slide, and the smear is prepared in the usual fashion. This method permits selectivity of cells collected, so that a large concentration of squamous cells from this key point may be studied while they are still in an excellent state of preservation before they have become shrunken or degenerated.

The essential nature of any cancerous growth contributes to the success of this method as these growths are characteristically friable. Therefore,

\*Aided by a grant from the Ortho Research Foundation, Linden, N. J.

In other types of surface cancers, e.g., tongue, lip, etc., the selective cytology smear may be taken simply by scraping the surface of the suspicious area. While such surface malignancies are readily accessible to surgical biopsy, the great advantage of the cytology technique lies in the fact that the cytology test is an office procedure, whereas biopsy may require hospitalization. An immediate presumptive cytology diagnosis will often obviate unexpected delays associated with later appointments or hospital bookings. In addition, cases arousing only slight suspicion in the physician's mind may require visual observation over a period of many months before slight suspicion becomes a positive conviction that a surgical biopsy procedure is indicated and justifiable. Such delays may be entirely prevented by the proper application of cytology methods.

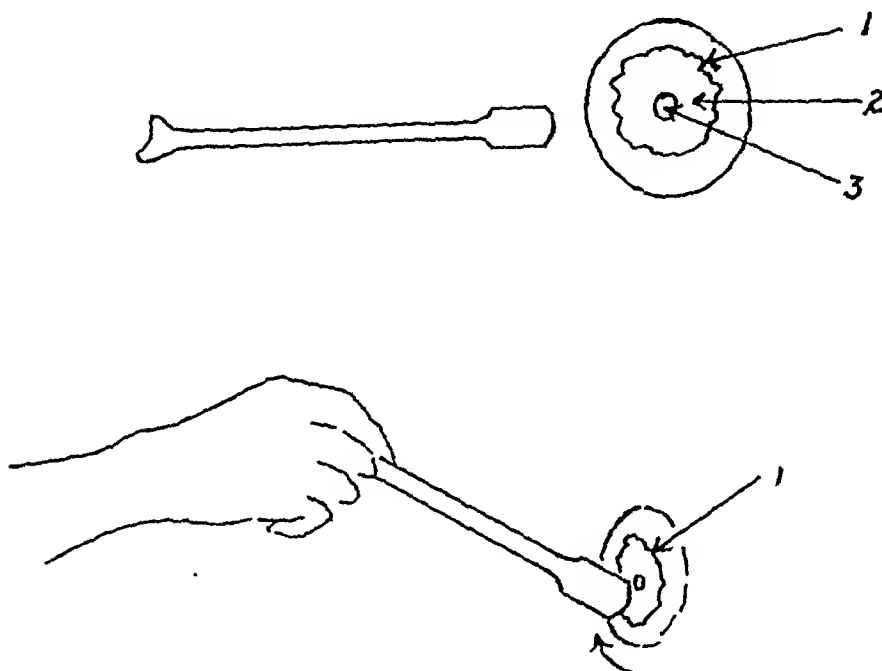


Fig. 3.—Technique for cervix with erosion, eversion, etc. (1) Squamocolumnar junction, (2) glandular epithelium, (3) cervical opening. Method of taking selective cytology test from cervix showing squamocolumnar junction located far out on vaginal portio distal to cervical opening, as in eversions, erosions, or extensive lacerations. End (b) is better suited to this type of cervix. All parts of irregular squamocolumnar circumference may be "surface biopsied," while the usual surgical biopsy may miss a small localized lesion.

### Interpretation

The diagnosis of cancer by cytology techniques signifies the recognition of cells showing morphologic characteristics consisting of extreme nuclear variability in size, shape, and in staining characteristics with occasionally multinucleation and mitosis. In other words, the diagnosis rests chiefly upon the recognition of individual cancer cells as such. Most malignancies are associated with bleeding and secondary infection, so that a great deal of purulent and sanguineous matter is thrown off from the growth. Therefore, red blood cells and leucocytes are almost invariably found in association with the malignant cells exfoliated from its friable surface. When the selective cytology technique is used in cancer cases, the only difference from the previous secretion-aspiration technique is that less blood and pus are encountered and more numer-



Parous cervixes more commonly exhibit a larger portion of the reddish glandular cervical epithelium, with or without an erosion, eversion, or laceration. For cervixes of this type the spatula test is taken by scraping along the squamocolumnar margin at the most suspicious area with the other end of the spatula (Fig. 1, *b*) just as a surgical biopsy site would be selected. The "sur-

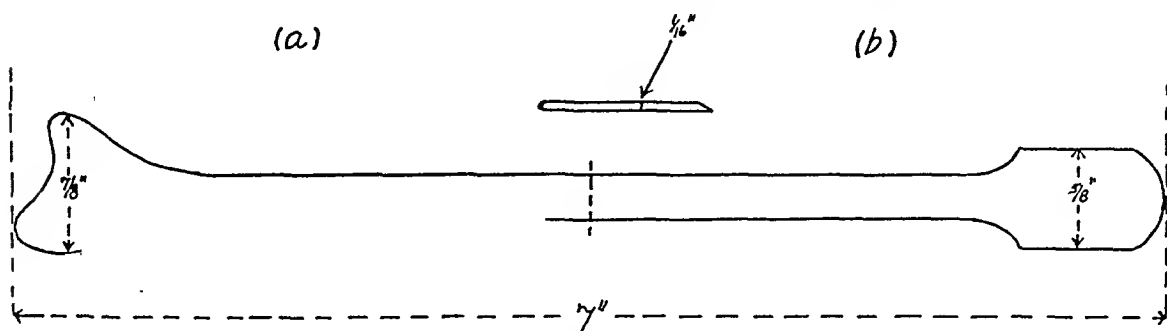


Fig. 1.—Wooden spatula for selective cytology technique. Either end may be used, depending upon the type of cervix. End (*a*) is best suited for nulliparous cervixes, or cervixes where the squamocolumnar junction is just outside the circle of the cervical opening. Placing the hook of the spatula in cervical os, a gentle rotation permits a light scraping of the entire squamocolumnar junction. The hook end is not suitable for cervixes with long erosions, as the scraping might miss the squamous tissue, obtaining a "surface biopsy" of glandular tissue only. In eroded, lacerated, parous cervixes, end (*b*) is more suitable.

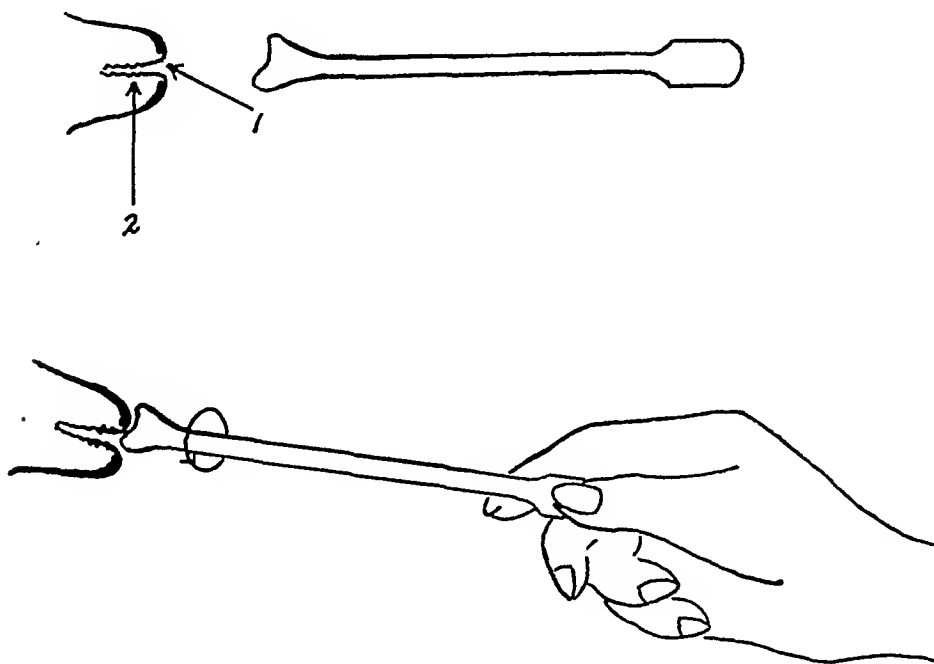


Fig. 2.—*Technique for nulliparous cervix.* (1) Squamocolumnar junction; (2) glandular epithelium. Method of taking selective cytology test in nulliparous cervix. Hook end (*a*) of spatula fits into cervix permitting gentle contact with squamocolumnar junction. By rotating spatula the entire circumference of this cancer zone may be "surface biopsied." The cells shed from this key point show the earliest indication of incipient carcinoma before any lesion may be recognizable to the naked eye.

face biopsy" need not be confined to one area, however, as the entire squamocolumnar margin may be investigated although this may require three or four separate approaches with the spatula in the presence of a large erosive zone (Fig. 3) with an irregular circumference.

The spatula procedure frequently will provoke slight bleeding, but this is usually transient and harmless.

to them, however, as the more bizarre and colorful nature of the specifically malignant cells has overshadowed them.

It has been our contention, following a cytological study of over 3,000 cases, that by the use of cervical cytology tests in general and the spatula technique in particular, that death from carcinoma of the cervix should be highly prevent-



Fig. 5.—Cervical cytology smear from case of squamous carcinoma of cervix. Numerous bizarre malignant cells as well as cells exhibiting precancerous morphology are noted.

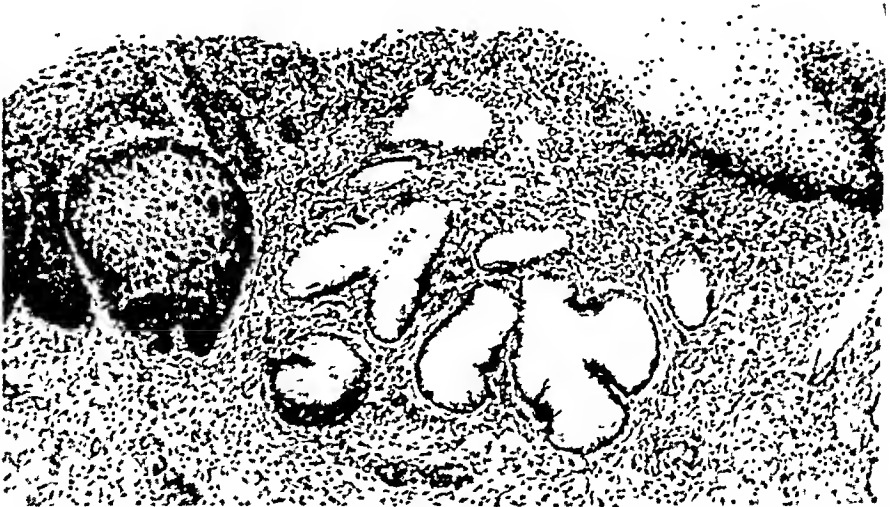


Fig. 6.—Cervical biopsy at squamocolumnar junction showing small intraepithelial squamous growth. Although this cervix appeared innocent, selective cytology smears detected cells of precancer morphology at the squamocolumnar margin.

ous clusters of the freshly shed malignant cells are available for diagnostic study.

The diagnosis of precancer demands not only the greatest precision in the taking of the test, but also precision in the interpretation of the morphologic indications which we have come to associate with this transitional or precursor stage of cancer. As described more fully in another publication,<sup>9</sup> the criteria in precancer consist in the detection of the following morphologic changes in the cells being desquamated at the squamocolumnar junction (Fig. 6):

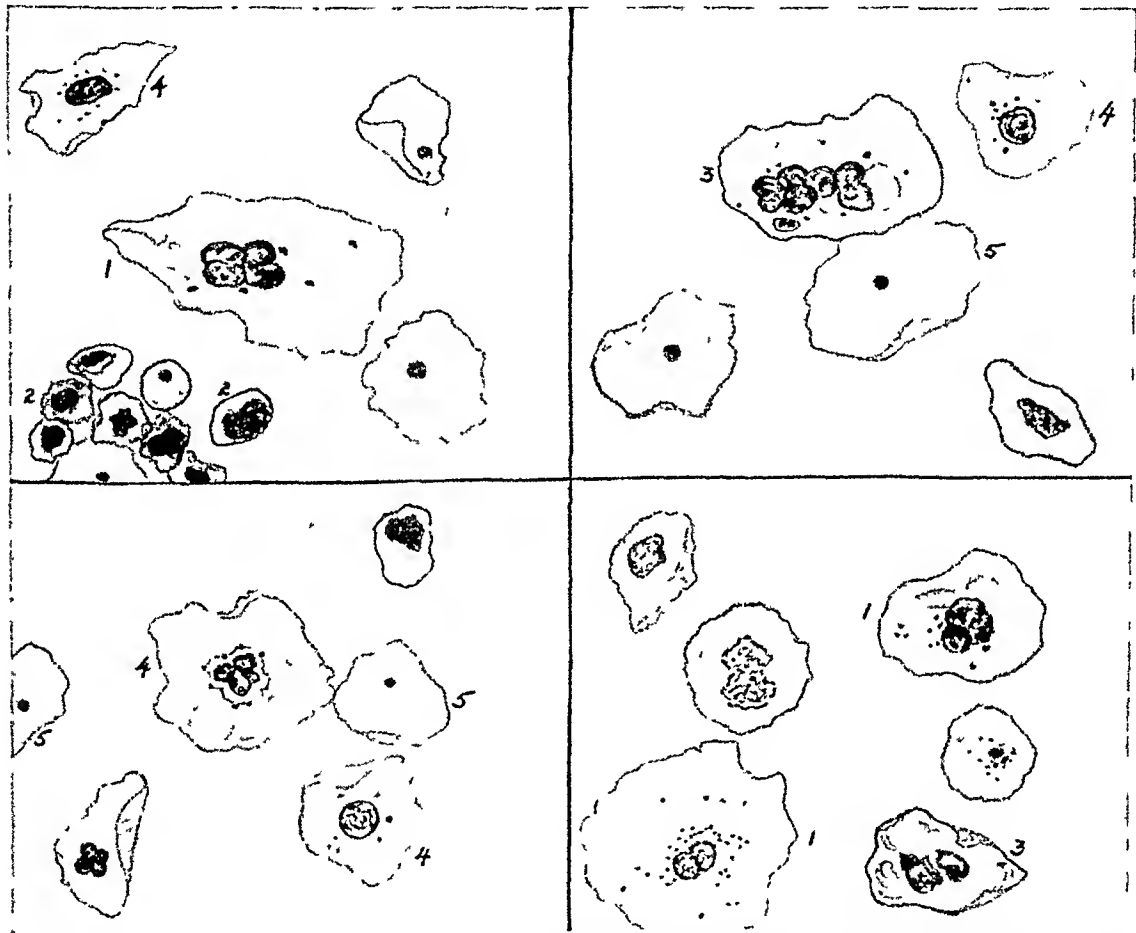


Fig. 4.—Precancer "cell-complex." (1) Multilobulated cells; (2) anaplastic deep squamous cells; (3) multinucleated cells; (4) cornified cells with abnormally large, pyknotic nuclei; (5) normal cornified cells (present in excessive numbers).

- 1: Cornified cells whose nuclei are abnormally large and deeply staining.
- 2: Multilobulation and splitting of the nucleus into several separate nuclei in cornified and precornified cells.
- 3: Anaplastic deep squamous cells showing considerable nuclear variability.
- 4: Abnormally high cornification.

Comparison of the types of cells found in cancer and precancer has revealed that cells of the precancer type are also to be found in smears taken from cases of full-blown carcinoma (Fig. 5). Little attention has been directed

Our experience to date has suggested that the appearance of the cervix clinically gives no indication of the intrinsic cell morphology. Many of the most suspicious-appearing lacerated, infected, eroded cervixes exhibit benign cytology findings, while conversely many normal-appearing cervixes show



Fig. 9.—Squamocolumnar area in same case (Fig. 8) showing hyperplastic anaplastic squamous changes.

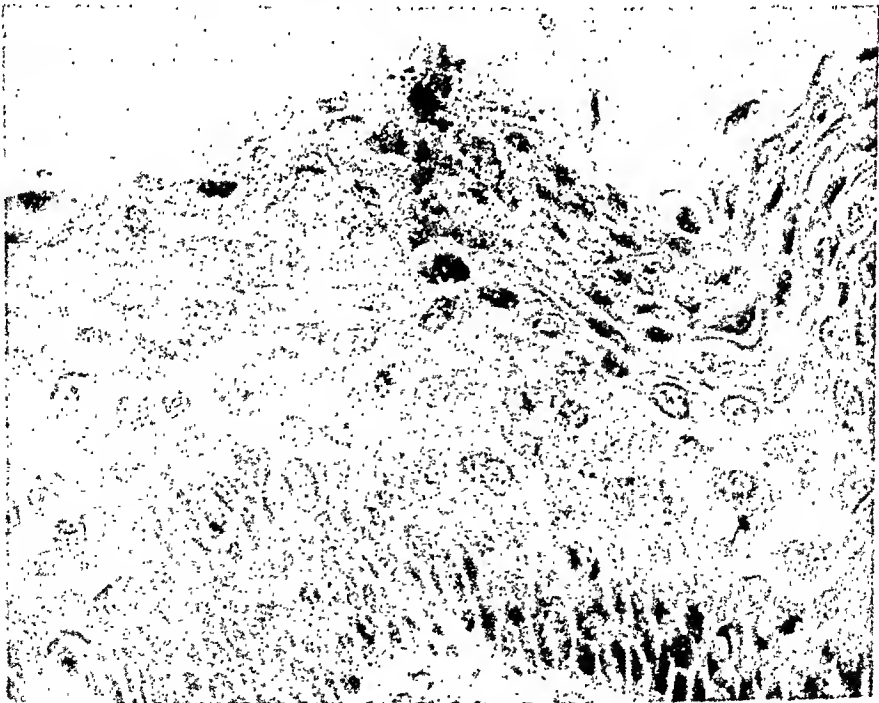


Fig. 10.—High power of squamous tissue (in same case as Figs. 8 and 9) in region of squamocolumnar junction. Observe intraepithelial changes and exfoliation of precancer cells along the surface.

able. This statement depends largely upon the fact that a diagnosis of cervical precancer is possible by this method. It should be stressed, however, that accuracy in interpretation of cytological evidence will depend upon the experience, skill, and judgment of the cytologist. It must be recognized before attempting cytological practice that it is a highly specialized technique requiring precision and care in the taking of the tests, skill in the staining with the excellent Papanicolaou\* stains, and experienced judgment on the part of the cytologist.

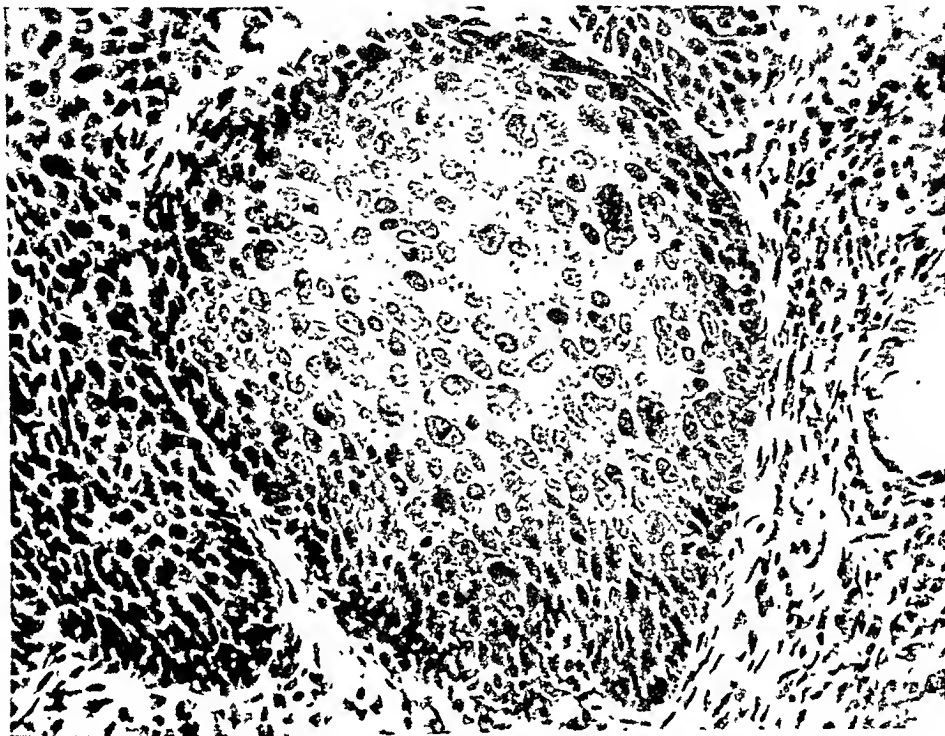


Fig. 7.—High power of suspicious intraepithelial growth shown in Fig. 6.

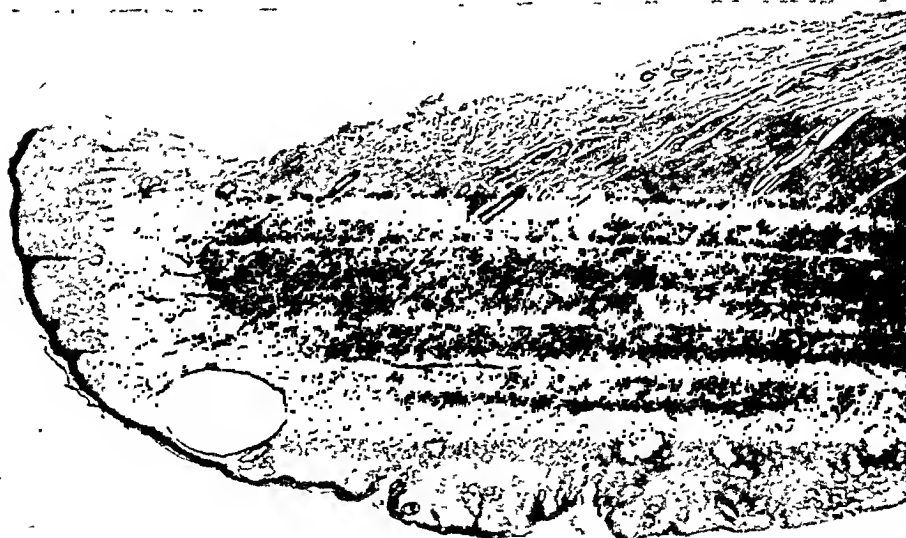


Fig. 8.—Cervical biopsy from young woman (30 years of age) complaining of intermenstrual bleeding. Selective cytology test diagnosed as precancer.

\*EA50 & OG6.

## OPERATION FOR THE CURE OF INCONTINENCE OF URINE IN THE FEMALE

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**I**NCONTINENCE of urine is a most distressing affliction. A minor degree is known as "stress" incontinence in which the leakage takes place on coughing, laughing, sneezing or descending stairs. Some women wet themselves only when the bladder is full and they, because of negligence or outside circumstances, cannot reach the toilet without delay. In major degrees of incontinence, all urine is lost while standing or sitting. In total incontinence the urine leaks even in the prone posture. This presentation does not include incontinence due to neurogenic causes or to bladder fistulas. The vesical neck weakness and insufficiency, I desire to discuss, usually results from birth trauma. Most often it is noted soon after delivery; in rarer instances the disturbance first manifests itself as the involution of the menopause develops. Intercurrent attacks of cystitis aggravate the symptoms. One instance of defective control due to congenital malformation is described. Incontinence is more frequent in the presence of cystocele and prolapse, but occasionally, and these are the most difficult to cure, little anatomic damage can be demonstrated.

Many operations for the cure of this disorder have been devised. This in itself bears proof to the fact that none of these interventions is completely effective. Attempts to describe the anatomy and the physiology of the bladder neck are not convincing (older literature, see Veit<sup>1</sup>; recent, see Martius<sup>6,7</sup> and Kennedy<sup>5</sup>). The simple reefing of the bladder neck by the "Kelly stitch" is the most usually employed maneuver, but this may signify anything from placing sutures haphazardly in the vicinity of the urethrovesical junction or to more thoughtful repairs such as that of Kennedy,<sup>5</sup> Frost,<sup>3</sup> etc. More complicated operations include Martius' bulbo-ovary flap,<sup>6</sup> Berkow's advancement,<sup>2</sup> or the Goebell,<sup>4</sup> Stoeckel<sup>8</sup> fascia slings or modifications thereof.<sup>1</sup>

My interest has been focussed particularly on the difficult cases in which one to three previous operations have been unsuccessful or actually aggravated the disability. Even in these cases I have found it unnecessary to resort to complicated procedures, obtaining satisfactory results by proper utilization of the locally available fascial structures. Fortunately, it appears that at previous interventions the essential connective tissue and fascial layers have been left intact or at least have not been destroyed. By careful exposure and preparation, especially difficult if previous operations have produced shortening and semicartilaginous scarring of the anterior vaginal wall, the bladder and urethrovesical junction are exposed. Three structures must be demonstrated and utilized.

1. The fascia propria of the bladder.
2. The pubo-ovarian layers of the endopelvic fascia.
3. The remains of the triangular ligament.

cytological evidence of early growth activity. How infrequently in gynecologic practice do we encounter an early cervical cancer which is recognizable clinically! Most of those which are recognizable are advanced and incurable. It would appear that only by routine cervical cytology tests, regardless of symptomatology, will it be possible to take advantage of the lifesaving possibilities offered by cytology.

### Summary

The selective cytology technique was developed in our search for a method of studying evidence of cancer growth in the cells which become earliest involved in cervical cancer.

The squamous cells encircling the tiny cervical opening at the squamocolumnar junction constitute a key point of origin for cancer more frequently than any other single focus in the female body.

The spatula test offers a technique providing "surface biopsy" information of these cells prior to their actual desquamation. (Other cytology techniques depend upon detection of cells already exfoliated into body secretions for cancer diagnosis).

By study of these cells in selective cytology smears, morphologic changes have been identified believed to constitute a precancer cell-complex. Many of these so-called precancer cases have shown clinically normal cervixes.

Biopsies have verified suspicious nature of lesions.

The selective cytology technique has been found to be more accurate as an indicator of endogenous estrogen by cornification counts in smears from the cervix and vagina in cancer cases. The previous aspiration method failed to reveal the true cornification level because of excessive amounts of blood and leucocytes obscuring the picture.

Selective cytology may be used in the diagnosis of any accessible surface cancer, e.g., tongue, lip, throat, skin, and vulva, while cytological cancer diagnosis of other organs, e.g., stomach, lung, prostate, kidney, and bladder, must depend upon other cytology techniques recently developed.

Through early diagnosis of cancer by routine cytology tests, death from cancer of the cervix should become highly preventable.

Miss Evelyn Dakin, Director of Technicians in the Gyne-cytology Laboratory, has been of invaluable assistance in the development of this cytology method. Dr. Paul Chevalier, Molson Fellow in Cancer Research, has also rendered valuable assistance in the preparation of this work.

Photomicrography by H. S. Hayden, F.R.P.A., and H. Coletta, McGill University.

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2. The separated and fully defined layer of the endopelvic fascia (pubo-cervical) is now approximated from below upward. The lowest two sutures, which include the "bladder pillars" tack the fascia to the anterior surface of the cervix, thus permanently elevating the bladder. The higher ones imbricate or overlap the fascia in front of the bladder. It will be found that the topmost suture brings together the fascia in a "V" shaped sling which is slightly higher up than the "V" previously formed by the fascia propria (Fig. 3).

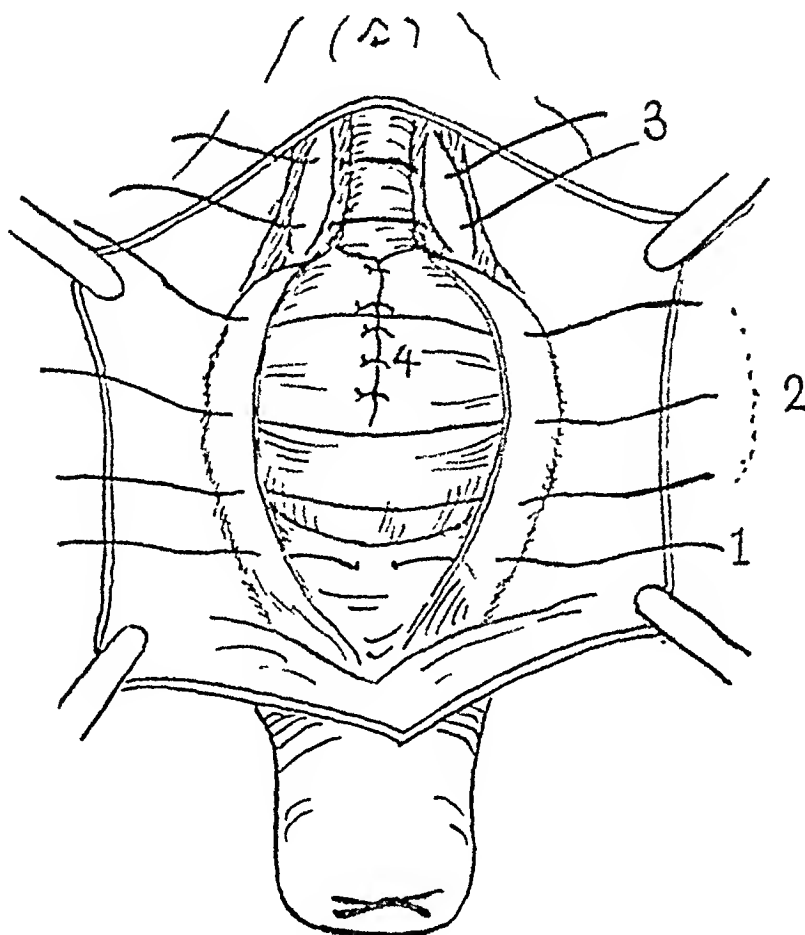


Fig. 2.—Sutures in situ.

1. Lowest suture which will tack down pubocervical fascia to cervical wall thus elevating bladder.

2. Additional sutures uniting pubocervical and vaginal fascias.

3. Sutures through torn fibers of triangular ligament—the last to be tied.

4. Sutures through fascia propria of bladder already tied. Note "V" shaped collar tight about urethrovesical junction.

3. The posterior and lateral surfaces of the lower portion of the urethra have been exposed and demarcated previously. Now the tissues lateral to the urethra beneath the pubic bones are grasped with a blunt hemostat on each side. These tissues are what remains of the triangular ligament. Sometimes a broad resilient struction is found; in others these tissues are tenuous but firm. Two chromic sutures are passed uniting the structures snugly in front of the urethrovesical neck (Fig. 4). If traction on the cervix is released, it will be found that the urethra, which previously sagged, now runs a straight course inward beneath the symphysis, and that there is a sharp angle where the bladder neck is situated (Fig. 5, c).



### Technique

A median vertical incision extending from 1 cm. below the urethral orifice down to the fixed portion of the mucosa over the portio is made through the anterior vaginal wall. The mucosal edges are grasped and, starting from below, the endovesical fascia and fascia propria of the vagina are peeled away from the vaginal mucosa in one layer, mainly by blunt dissection. Inferiorly these layers are found to terminate in the bladder pillars (Fig. 1); above they thin out and disappear at the level of the urethrovesical junction.

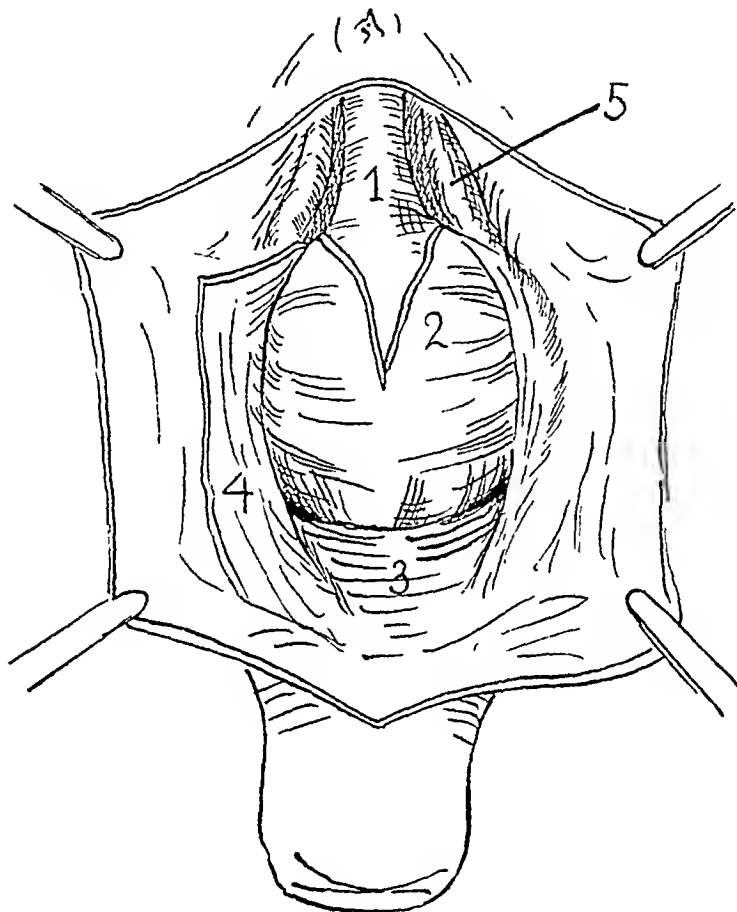


Fig. 1.—Exposure of urethra and bladder through longitudinal incision.

1. Urethra.
2. Fascia propria of bladder with "V" shaped defect superiorly.
3. Anterior wall of cervix after bladder has been liberated.
4. Pubocervical fascia (endopelvic fascia) fused with vaginal fascia.
5. Remains of triangular ligament under pubis. (See Fig. 5, C).

When this dissection has been completed on both sides, the bladder is freed and mobilized from the cervix and lower uterine segment in the customary way. In previously operated upon patients this separation may have to be performed by tedious sharp dissection, and requires extreme care in order not to injure or perforate the vesical wall.

1. Examination of the liberated bladder will show that the fascia propria of the bladder, a thin but strong layer, inseparable from the bladder wall, is defective at the bladder neck. By placing interrupted sutures of fine chromic gut which are started at least 5 cm. below the vesical neck and proceeding upward, a definite "V" shaped collar is formed at the urethrovesical junction, tight enough to indent the urethral tube slightly (Fig. 2).

The operation is concluded by resecting the vaginal edges, if this is indicated, and closing the vaginal wound with interrupted sutures.

I insert a rubber open-end catheter and leave this in the bladder for five days. The bowels should be constipated for the same period. The patient gets out of bed on the tenth day.

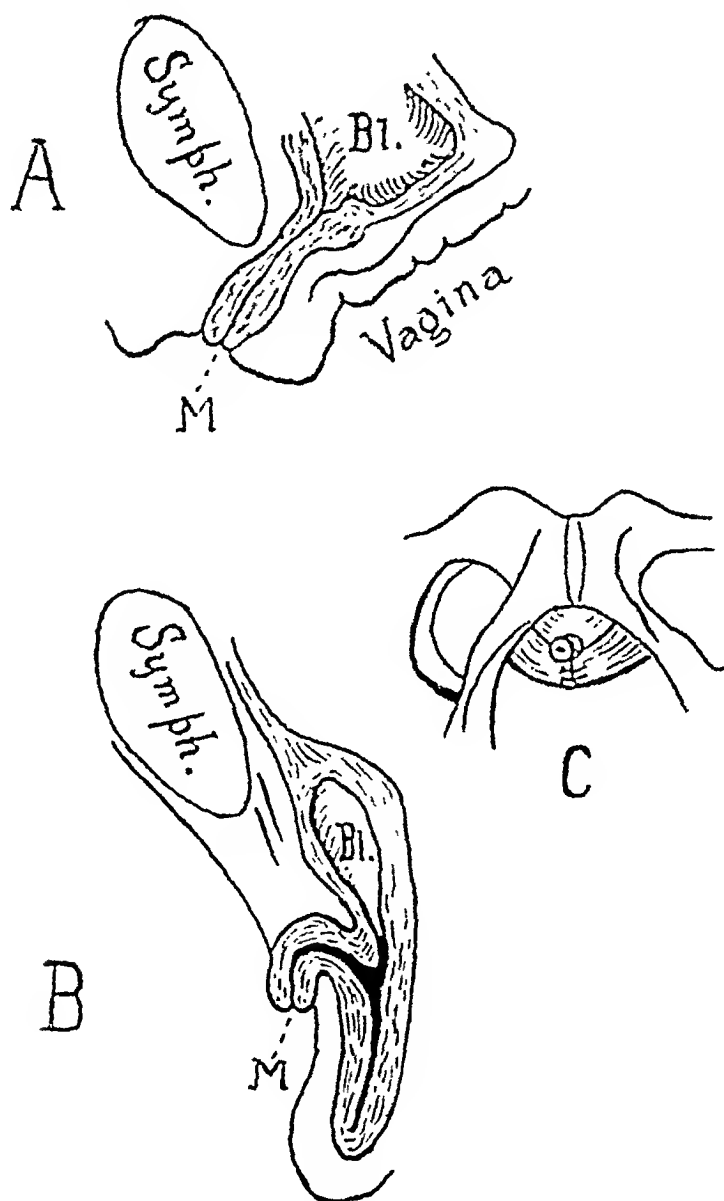


Fig. 5.—A. The urethra runs normally beneath symphysis, bladder in normal position. Such relations may persist in the presence of uterine prolapse. M = Meatus urinarius.

B. Sagging away of urethra in some cystoceles and cystoceles with uterine prolapse. Note increased separation of urethra from symphysis, drooping course, as well as descent of bladder, in cystocele.

C. Symphysis pubis and rami showing course of urethra after repair of triangular ligament. Compare with Fig. 4.

### Discussion

I have used this simple but precise technique for years with satisfactory result for both stress and complete incontinence. I have collected nineteen private patients upon whom this operation was performed in the last ten years.

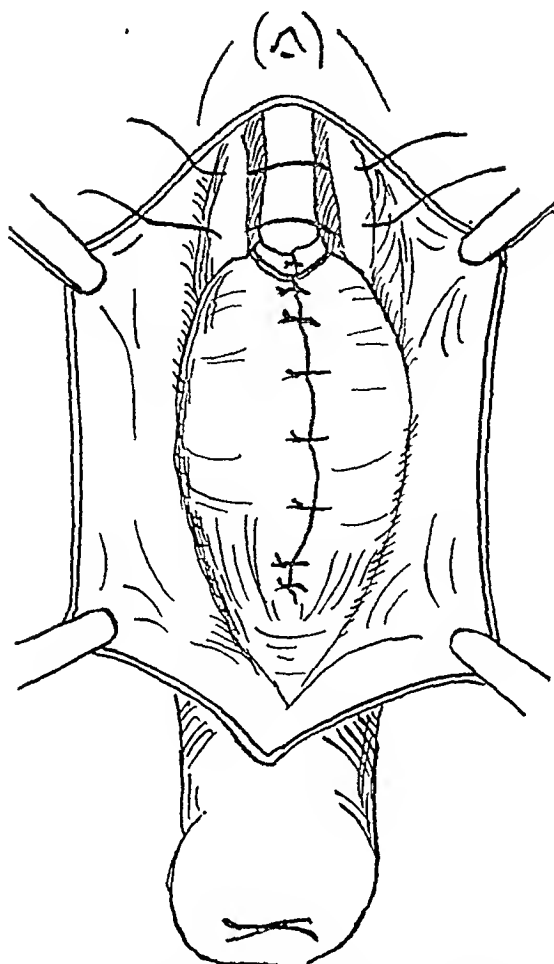


Fig. 3.—Tying of pubocervical fascia sutures has elevated and retained bladder and formed another fascial collar at urethrovesical junction. Triangular ligament sutures placed but not tied.

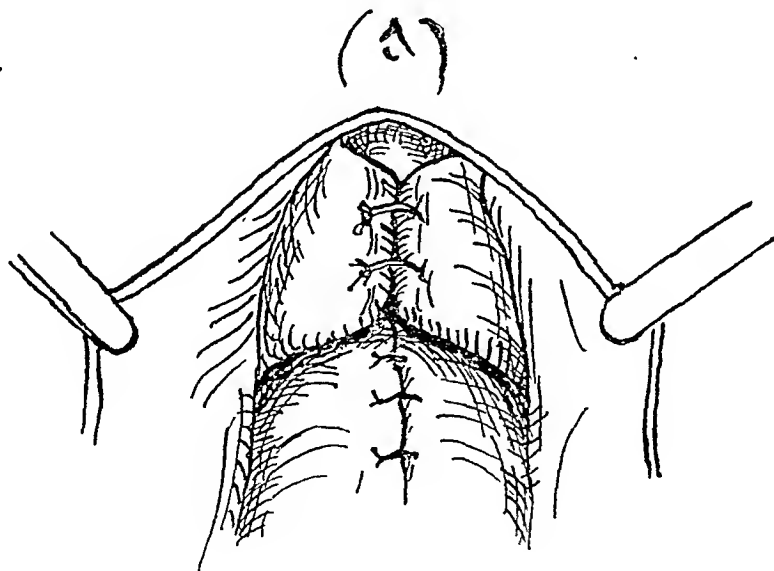


Fig. 4.—Triangular ligament sutures tied anterior to urethra; below these are the pubocervical sutures also tied. Upon release of traction on cervix the urethra will retract snugly under symphysis as in Fig. 5, C.

TABLE I

	NAME	AGE (YEARS)	PARITY	LAST CHILD (YEARS)	SYMPTOMS	OPERATION	RESULT	REMARKS
1	Wa., S. '36	32	2	24	Feeling descent; stress incontinence; cysto-rectocele	Anterior and posterior colporrhaphy; ligation tubes	Cured	Follow-up 2½ years
2	Ba., I. '37	52	3	13½	Incontinence on walking; no rectocele	Anterior colporrhaphy	Cured	Local infiltration anesthesia
3	Lo., A. '38	12	0	0	Incontinence urine and stool, congenital	Urethro and anal plastics	Incontinence urine cured; alvae improved	Congenital
4	An., A. '42	40	2	12	Stress incontinence; relaxed anterior vaginal wall	Anterior and posterior colporrhaphy	Nearly 100%	
5	Th., B. '42	60	2	28	Stress incontinence; cystocele; slight descent	Anterior and posterior colporrhaphy	Cured	
6	Ke., C. '43	49	3	19	Stress incontinence; cysto-rectocele; fibroids	Anterior colporrhaphy, vaginal hysterectomy morcellation	Cured	Posterior colporrhaphy not done as shock developed
7	Ha., S. '43	70	6	34	Hugo cystocele; rectocele; stress incontinence	Anterior and posterior colporrhaphy under local	Unimproved	Fair anatomical result. Stress incontinence unchanged
8	Wa., M. '44	50	2	21	Stress incontinence; no cysto-rectocele	Anterior and posterior colporrhaphy	Cured	
9	Mo., H. '45	46	2	22	Stress incontinence; moderate cysto-rectocele	Anterior and posterior colporrhaphy	90% improved	Slight wetting on heavy coughing. Formerly on walking

Of these, four had had from one to three previous plastic operations without cure (Table I). Two of them were cured, two 75 per cent improved and fully satisfied. The fifteen remaining showed twelve cured, two 95 per cent improved (patient's estimate), one unimproved (age seventy years). One patient developed urge and urinary pain, later cystoscopy by Dr. H. E. Leiter showed polypi around the internal sphincter of the bladder. A few of the case histories are of sufficient interest to warrant brief description.

CASE 3.—A. L., aged 12 years. Born with vaginal anus. No control of urine or feces. At 2 years anus transplanted but still too far anterior. Urethral opening far back, lax. At operation posterior urethra and bladder neck exposed, fascias approximated. Then anus retransplanted posteriorly into anal dimple. Full urinary continence. Improvement of rectal control.

CASE 13.—Complete incontinence for twenty-five years. Eight years ago vaginal plastic was performed, incontinence unimproved. Four years ago a plastic was performed, with no improvement. Three years ago the patient had a complete abdominal hysterectomy, with no improvement. Patient was 45 years old, short, obese, and weighed 240 pounds. Tight introitus, urethra in normal site, no descent of anterior vaginal wall. Blindly ending vagina.

Incision from just below meatus to below neck of bladder. Careful reefing of fascial layers. Fully continent for days. Then coughing spells (allergic) with slight wetting.

CASE 11.—Patient was 52 years old; had had a plastic performed twenty years ago, and two in 1943. Wet except in bed. Weight 175 pounds. Cervix descended to weak perineum. Fundus small and in midposition (menopause of one year duration). The anterior vaginal wall was flat, scarry, and mucosa atrophic.

The broad boardlike scar in the vaginal wall was excised. Bladder was mobilized by sharp dissection, and the urethra freed with difficulty. Then careful fascial suture. Improvement 75 per cent.

When a first to third degree prolapse exists, parametrial fixation (Manchester operation) with preliminary exposure of the fascial planes (*vide ante*) and careful suture should give 100 per cent of cures (Cases 16, 18, and 19). Vaginal hysterectomy when indicated, if the bladder and fascias are exposed before the parametria are cut, likewise offers sure prospect of cure (Case 6). On the other hand, vaginal interposition of the fundus may jeopardize full control. In Case 14, the patient, on first getting out of bed, had poorer control than before her operation. Three weeks later control was complete. This coincided with a slight slipping back of the interposed fundus.

With the exception of one patient (Case 7), all were so well satisfied with their control that I have not had the occasion or necessity to reoperate upon any of these women. In Case 7 I refused to attempt further intervention—age 70 years, orthopnea, necessity to let patient out of bed on first day.

The final result depends not upon suture material, overlapping, type of denudation, etc., but upon exposure and utilization of three fascial structures—fascia propria vesicae, pubocervical fascia, and triangular ligament.

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### Addendum

Since submitting this manuscript, I have operated upon four more patients—one Manchester procedure, one anterior and posterior colporrhaphy, and two anterior repairs. Three were cured. The fourth, a woman five feet tall, who weighed 253 pounds, and who had complete incontinence (two previous plastic operations), some days has perfect control, other days is incontinent.

10	Sc., K. '45	51	4	23	Stress incontinence; large rectocele; no cystocele	Anterior and poste- rior colporrhaphy	Cured	
11	Li., A. '45	52	2	30	Wet except when prone; flat scarry anterior vaginal wall	Anterior colporrha- phy, excision scar, etc.	75% improved	Three previous plastics; 20, 3, and 2 years ago
12	Li., B. '45	48	2	14	Stress incontinence; billion ball cystocele	Anterior and poste- rior colporrhaphy	Cured	Menopause at 45 years. Cataract operations Two previous plastics.
13	Wa., A. '45	45	?		Incontinence 25 years; no cystocele	Anterior colpor- rhaply	Cured	Complete hysterec- tomy. Weight 240 lbs.
14	Ra., S. '45	52	2	23	Stress incontinence; cystocele	Interposition, ante- rior and posterior colporrhaphy	Cured, polypi around sphincter int.	
15	Kr., N. '46	47	3	18	Urge incontinence; short anterior wall; some prolapse	Anterior and poste- rior colporrhaphy	75% improved	Three previous plastics; 14, 12, and 4 years ago. Weight 200 lbs. No control if urge
16	Wi., J. '46	60	4	20	Dribble constant; cysto- cele and descent	Parametrial anterior and posterior col- porrhaphy	Cured	Plastic 1937, 1939
17	Go., P. '46	46	2	14	Complete incontinence for 12 years	Anterior colpor- rhaply	Cured	
18	Le., M. '46	38	3	7	1st degree prolapse; cystoectocole; com- plete incontinence	Parametrial, anterior and posterior col- porrhaphy	Cured	Full control; has had one attack of cystitis since operation
19	Bl., M. '46	36	2	5	1st degree prolapse; cystoectocole and stress incontinence	Parametrial, anterior and posterior col- porrhaphy	Cured	

Irregular shedding of the endometrium is, then, a condition in which there is a disturbance of menstrual bleeding and is clinically characterized by various degrees of prolongation or profuseness of menstrual blood loss. It is characterized histologically by variations from the normal of the menstrual processes of shrinking, shedding, involution, and healing of the endometrium. Evidence will be presented to suggest that the condition is characterized endocrinologically by an abnormal persistence during the bleeding phase of the excretion in the urine of sodium pregnandiol glucuronide. It appears, then, to be a specific entity.

It will serve the present purposes to conclude arbitrarily that the process of menstruation involves withdrawal of hormonal support of the endometrium. This acts through spasm of the coiled arterioles to produce various end results which include shrinking, shedding, and involution. Healing is dependent upon the efficiency of these three processes. Too little is known of what happens to the coiled arteriole itself, but it is instructive to observe these in abnormal states.

These features show some variation in normal menstruation. When they are seriously disturbed, the end result is prolonged and profuse menstrual blood loss. It is this condition to which the term irregular shedding has been given.

### Clinical Features of Irregular Shedding

Thirty-four cases have been taken at random and form the basis of the following conclusions: The condition may occur at any time during active sex life. In the present group, the age of onset was less than 25 years in 3, from 25 to 29 years in 6, from 30 to 34 years in 5, from 35 to 39 years in 8, from 40 to 44 years in 9, and 45 years or over in 3.

There is little evidence of an effect of childbearing. Four were nulliparas, 16 had had from 1 to 3 pregnancies, 11 had had 4 to 7 pregnancies, and 3 had been pregnant 8 times or more. It is interesting to note, however, that in 9, the onset was at the time of the re-establishment of menstruation following a pregnancy. The frequently occurring profuse and prolonged menstruation for the first few menses after delivery or abortion appears to be due to irregular shedding. Few of these will be proved without special procedures. Since the expectation is that the majority of these patients will eventually establish normal menstruation, there is no reason to interfere and few will be discovered. This form of irregular shedding seems to be in some way different from that which occurs without association with the pregnancy or that which begins with pregnancy and persists for a long time. Most of those beginning with pregnancy disappear without specific therapy. The occasional patient who bleeds sufficiently with the establishment of menstruation post partum to require curettage will most often establish normal menstruation following a curettage done soon after the onset of the condition. If, however, the menorrhagia has begun post partum and has persisted for six months or more, it follows the clinical rules of the general group. The histologic features of the endometrium of the postpartum irregular shedding are similar to those of the general group.

Statements as to the duration of the bleeding will to some extent depend upon the individual physician's arbitrary standards as to what constitutes an abnormal condition and so justifies study. In the present group, 15 bled for



## IRREGULAR SHEDDING OF THE ENDOMETRIUM\*

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**I**RREGULAR shedding of the endometrium is a condition associated with the prolongation of menstruation and an increase in the amount of blood loss.

Since one form of disturbed menstruation is to be discussed, and since some confusion now surrounds the significance of the term menstruation, it becomes necessary to describe the sense in which it is used in this presentation. To the clinician, a normal menstrual cycle is one in which there is reason to believe that ovulation has occurred and in which the endometrium is prepared to receive the fertilized egg. By normal menstruation, he means the series of events which occur at the end of such a potentially fertile cycle when conception has, for one reason or another, not occurred. This is what Corner has been pleased to call "the German theory." So far as the endometrium is concerned, one may define normal menstruation as uterine bleeding associated with the shrinking, shedding, and involution of an endometrium which has been specifically affected by estrogen and progesterone from the natural source. Irregular shedding of the endometrium is a term which has been coined to describe one abnormal form of menstruation as so defined.

The second general principle, applicable to a consideration of irregular shedding and differentiating it from normal menstruation, has to do with the quantity and duration of the blood loss and is not so easy to define. The quantity of blood loss may be expressed in terms of the measured quantity which is lost, the effect upon the hemoglobin content of the circulating blood, and the degree of disturbance of various features of the welfare of the patient concerned. While one of these measures may on occasion be enough to convince the observer that he is dealing with what must be considered a pathologic condition, it is more usual that all must be taken into consideration. What will be withstood, repaired, or tolerated by one individual may well cause another to justifiably seek and demand relief. By and large, menstrual bleeding which lasts beyond seven days and is sufficient in quantity to lower significantly the hemoglobin content of the blood or to produce subjective symptomatology in the patient is abnormal, although the individual patient and physician will be quite justified in setting their own standards when the degree of the condition is mild. One need not be too disturbed with this, since what is being dealt with in irregular shedding is an objectively controllable disturbance of mechanism and endocrinologic background and what is, for the most part, a gross disturbance of the quantity and duration of the menstrual blood loss.

\*Presented, by invitation, at a meeting of the Chicago Gynecological Society, Nov. 22, 1946.

a year later curettage yielded a diagnosis of characteristic endometrial hyperplasia. Hysterectomy was carried out and a broad based myoma was found filling the uterine cavity.

### Histologic Characteristics and Diagnosis

The literature dealing with the subject has been reviewed in a previous publication. As in all abnormal uterine bleeding, histological study offers the essential and indispensable control. This is obtained by curettage. In order to arrive at a histologic diagnosis, however, the clinician must understand the nature of the condition in order that he may time his curettage so that material may be obtained which is suitable for histologic study. Irregular shedding of the endometrium is essentially a prolongation and irregularity of the various features of normal menstruation. Ultimately, healing of the endometrium takes place and there is little in the healed endometrium of the nonbleeding phase from which the histologist can make an accurate diagnosis. The endometrium of the first few days of bleeding is so similar to that of normal menstruation and its normal variations that an accurate diagnosis is at best difficult. The endometrium should be taken on the fifth day of bleeding or later, depending somewhat upon the expected duration of the flow. The histologist's problem will be simpler and his conclusions more accurate if the endometrium is obtained well before the end of the expected bleeding when this is excessively prolonged.

The histologist's problem is the recognition of the gross irregularity of the various features of the menstrual endometrium, but he must also be prepared to compare these findings with those which are within the normal range of variation for a similar day of bleeding. The clinician, then, must supply the histologist with information as to the day of the bleeding upon which the material was obtained, and the histologist must use this information.

It is not possible to lay down accurate histologic features which will be reproduced in each endometrium of irregular shedding. Healing ultimately occurs and the time required to bring this about varies from one patient to another. The point of time within this process at which the endometrium is taken will govern the degree of the various abnormalities and their persistence.

In general, the outstanding feature of the endometrium of irregular shedding is its irregularity. Endometrium which has functioned (secretion phase) is retained and very little surface epithelium or none at all may be seen at a time perhaps long after healing should have taken place. Secretion phase or functioning epithelium may be present in one piece of endometrium while proliferation phase characteristics may dominate another. The glands will vary from straight tubes to those with dilated lumina and irregular margins. The stroma is usually shrunken and cellular, and may show a circular arrangement about the glands which is peculiar to this condition. Except for endometrium which is taken relatively early in the bleeding, it is unusual to find much persistence of the intercellular edema and large pale cells with relatively pale nuclei which are characteristic of the secretion phase stroma. When this does persist, it seems to occur in the neighborhood of blood vessels.

from 7 to 10 days, 9 bled from 11 to 14 days, and 10 bled for 15 days or more of the cycle. These are somewhat dogmatic figures, since the duration of bleeding may vary from one menstruation to another. The figures used for the statement of duration were composed of an average for each patient.

In all patients, the bleeding was profuse, and this was confirmed in most of them by inquiry as to the details of this. In some, it was very profuse. Hemoglobin determinations as low as 5 Gm. per 100 c.c. of blood were found. The majority showed only minor degrees of anemia.

Earlier in this work it was thought that the duration of the cycle was not disturbed. This has not proved to be the case. In 17, the cycle recurred at intervals of 25 to 35 days, and they were considered normal cycles. In 8 the cycle was less than 25 days, and in 9 the cycle was too irregular to classify. The cycle is disturbed, then, in half of the patients.

Study of the associated pathology is of interest. In interpreting this, it must be remembered that objective controls of the irregular shedding are available in the histologic characteristics of the endometrium and, in a limited number of the cases, of the endocrinologic background.

Of the 34 patients, four gave a history of previous surgical interference with tubes, ovaries, or both. The nature of the pathologic lesions requiring this was impossible to ascertain in some. It has long been recognized that endometrial hyperplasia not infrequently follows such surgical interference. Apparently, it can also give rise to irregular shedding.

One patient was found to have an endometrial polyp. Three had or had had thyroid disturbances. Two of these had basal metabolic rates of -22 and -14, respectively. Correction of this and curettage stopped the menorrhagia in one but was not effective in the other who eventually required hysterectomy. Of the other two, one had had a toxic adenoma previously removed and the other had had a thyroidectomy three years before because of thyrotoxicosis. A number of other apparently unrelated pathologic conditions were discovered in the group.

Nine of the patients, approximately a quarter of the group, had uterine myomas. Subserous, intramural and submucous myomas were all found. Some of these were very small. One myoma was removed by vaginal hysterectomy and the patient required no further therapy. In four of the patients, curettage alone was sufficient to allow the re-establishment of normal menstruation, and two of these were followed for two years. The significance of the association of myomas and irregular shedding is not altogether clear, and further information is required. It has a bearing upon a number of clinical problems, not the least of which is the irradiation therapy of myomas. The presence of myomas does not necessarily mean that they are the cause of an abnormal bleeding.

Two patients of the group had episodes of endometrial hyperplasia. One of these, a 45-year-old para iii, had had one tube and ovary removed fifteen years before, apparently because of inflammatory disease. She was admitted on the forty-third day of bleeding, and curettage showed an endometrial hyperplasia. Following this, menses were normal in quantity, duration, and interval for thirteen months, when two periods of bleeding of twenty-one and fourteen days, respectively, occurred. She was curetted on the fifth day of the next bleeding and characteristic irregular shedding was demonstrated.

The second patient was a 37-year-old para iii. Menstrual periods were normal until a year before admission when they began to become profuse and prolonged until they were recurring at 28-day intervals, were very profuse, and lasted for twelve to sixteen days. Curettage showed a submucous myoma and an irregular shedding. Profuse and prolonged bleeding persisted, and

irregular shedding there is some external interference with the process. Surface epithelization cannot occur until involution of retained stroma, glands, and epithelium which have functioned, is well advanced. Involution of retained coiled arterioles of the functionalis is either incomplete or cannot occur at all, although a conclusion in this case must await further study.

Illustration of the histologic findings in the cases to be described is omitted for lack of space.

### Etiology

The etiology of irregular shedding of the endometrium is not yet clear. The most likely explanation is that it is caused by a disturbance of endocrine control. Attempts have been made to study the blood levels of prolactin and estrogens. Too much blood is required to allow of more than occasional determinations. Other methods are more likely to yield reliable information in view of the known variations of these substances in different individuals, in one individual in different cycles, and at different parts of the same cycle. With the cooperation of Dr. L. T. Samuels of the division of Biochemistry of the University of Minnesota Medical School, the urinary excretion of estrogens, 17-ketosteroids, and pregnandiol was determined over at least a full cycle in six patients upon whom a histologic diagnosis of irregular shedding of the endometrium has been made. Estrogen and 17-ketosteroid excretion was normal in all. In five of the six, pregnandiol was excreted during various parts of the menstrual bleeding. This has not been found in any other naturally occurring condition than irregular shedding, although it may be produced by the artificial exhibition of progesterone during the bleeding or of gonadotropic substances toward the end of the premenstruum. In the one case in which it was not recovered, the patient had been bleeding profusely for a maximum of fourteen days of a 23- to 25-day cycle. Curettage established the diagnosis, and the endocrine excretion was studied during the following cycle. This ended in a six-day bleeding of normal quantity. One can only speculate as to the reason for the absence of pregnandiol excretion during this menstruation. The excretion of pregnandiol during the menstrual bleeding seems to be characteristic of irregular shedding, to set it apart from other known endocrine disturbances, and to suggest that it is a specific endocrinologic entity.

### Treatment

No specific treatment can at present be recommended, although it is obvious that a large part of the interest in the study of this condition is pointed toward the hope that a simple therapeutic solution might be indicated. It has been the policy of the department to curet these patients for both diagnosis and treatment and to repeat it if necessary. Observation of the results will allow a decision as to whether or not more radical therapy is indicated. In the younger patients, every possible avenue is explored. Other abnormalities are searched for and treated. The general physical status of the patient is improved by control of exercise, food, and general hygiene. In particular, anemia is actively treated. Curettage is repeated as indicated. This has been

There may be, then, an irregular and scattered persistence of epithelium and stroma with secretion phase changes interspersed among areas of endometrium which show regeneration.

More characteristic still is the presence of evidence of incomplete involution of all endometrial elements. These are characteristic of neither secretion nor regeneration or proliferation phase and produce bizarre pictures which add to the general impression of irregularity. Shrunk but still large stroma cells may be seen. Cellular and shrunken stroma may produce the circular condensation described about glands which are collapsed and often star shaped. The glands themselves may be dilated and tortuous in a stroma which has lost the secretion phase characteristics. The gland lumina may, on the other hand, be small but lined by epithelium which shows obvious evidence of having functioned. The epithelium itself presents a wide variety of characters. Full-blown late secretion phase change is seldom seen. These cells are low, having shed a majority of their cytoplasm, and have basally placed round pale nuclei. Clear spaces may be visible between the nuclei of contiguous cells. Histochemically demonstrable glycogen is present in the cytoplasm of such cells. If the endometrium be taken late in the bleeding, much of the epithelium may show the characteristics of regeneration with tall cells with little cytoplasm and basally placed tall nuclei, rich in chromatin, which are so tightly packed that they appear to overlap one another so that clear cytoplasm cannot be seen between them. Glycogen cannot be demonstrated histochemically in these. More characteristic of irregular shedding is the presence of epithelium which is in process of involution and which gives the impression of having difficulty in accomplishing it. Tall cells with much cytoplasm are seen. These have clearly not cast off their cytoplasm into the gland lumen. The nuclei are spaced so that clear areas appear between. They may be more or less centrally placed in the cell with collections of glycogen between them and the cell base. Variations between this picture and regeneration phase characteristics may be seen.

These peculiarities, irregularly scattered through a single endometrium, produce a bizarre picture which cannot be readily confused with any normal phase of menstrual shedding or repair. In some way, they interfere with surface epithelization or healing so that uterine bleeding persists.

Finally, it is possible to list at least some of the basic endometrial features of menstruation in the order of the efficiency or ease with which they are accomplished in irregular shedding. This is of some use in interpreting the histologic findings in material upon which a diagnosis is to be made. It is evident that shrinking of the stroma occurs readily. Involution of the stroma cells occurs almost as easily, so that even in the presence of marked evidence of function in glands and their epithelium the stroma is usually made up of small cells with little cytoplasm and with chromatin rich nuclei. They are closely packed to produce a dense cellular tissue. It is only occasionally that much intercellular edema or large pale stroma cells are seen in irregular shedding. Involution of glands and their epithelium seems to take a midposition. While this can eventually complete itself, one gets the impression that in

An untimed curettage was done with a diagnosis of premenstrual endometrium. Following this, the cycle returned to twenty-eight days, and there was some decrease in the amount and duration of bleeding. Two months before admission, bleeding lasted for four weeks. Bleeding began again and curettage was carried out on the seventh day of bleeding. Bleeding ceased eight days later to recur after an interval of seventeen days. This lasted for eleven days.

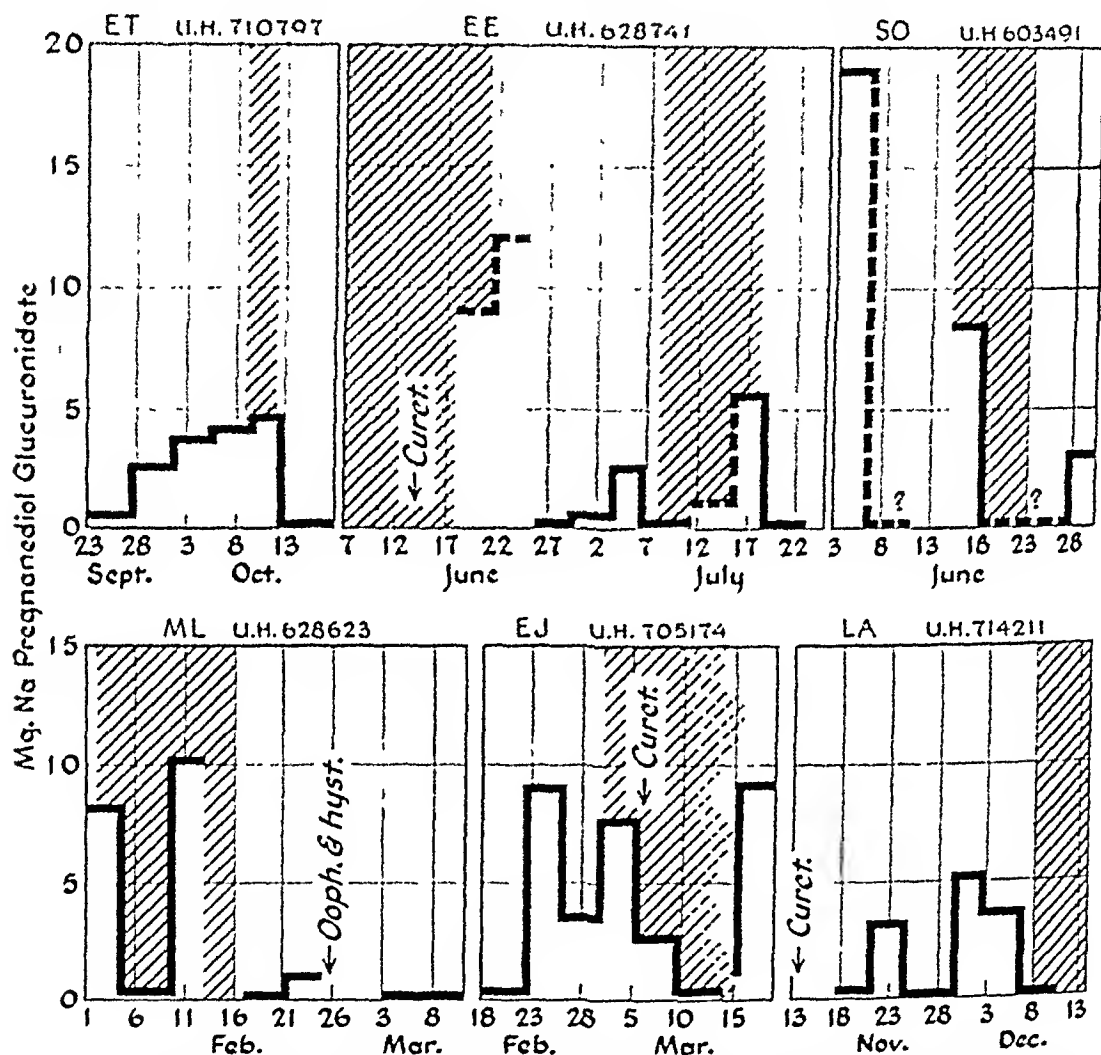


Fig. 2.—The excretion of pregnandiol in the urine in six patients, all of whom yielded histologic evidence of irregular shedding of the endometrium. Estrogen and androgen excretion was studied at the same time and was normal so that this is not illustrated. The determination of pregnandiol was carried out by the method described by Venning. All possible checks, including the routine determination of melting point, were used to assure the reality of the findings. Where any doubt whatever existed, the results are recorded in the illustration by interrupted lines.

All patients who had a histologic diagnosis of irregular shedding of the endometrium and on whom adequate excretion studies could be obtained showed pregnandiol to be excreted during some part of the bleeding phase, with the exception of Mrs. L. A. For details of this, see her case history.

What was probably pregnandiol was excreted in considerable quantity following curettage. It was present again during the last bleeding.

The uterus was eventually removed. It showed two small submucous myomas, one 2 cm. and another 1 cm. in diameter. There was no other pathology.

CASE 3.—Mrs. S. O. (U. H. No. 603491), a 45-year-old para 3-0-0-3. Menses were normal to 1939. She then occasionally missed a period and did not men-

only partially successful. In the series of 34 patients, the onset of the condition occurred before 30 years of age in nine. Curettage and general therapy were all that was required in seven, and in three of these the result was entirely satisfactory over short periods of observation. Two of these three later became pregnant. In one other patient, the menorrhagia persisted much as before treatment. In one patient, no result was obtained, and hysterectomy was eventually carried out.

In the older patients, and particularly in those past forty years of age, x-ray sterilization is the method of treatment of choice after failure of simple measures. Surgery is only resorted to when circumstances such as the youth of the patient require preservation of ovarian function or where other pelvic abnormalities such as large myomas make this the method of choice. Of the group of 34, seven were treated surgically, and five by x-ray sterilization. The remaining 22 received only curettage and nonspecific therapy. Follow-up studies are not complete, and it is possible that some of these 22 were treated by other means elsewhere. It is unlikely that this occurred in a significant number.

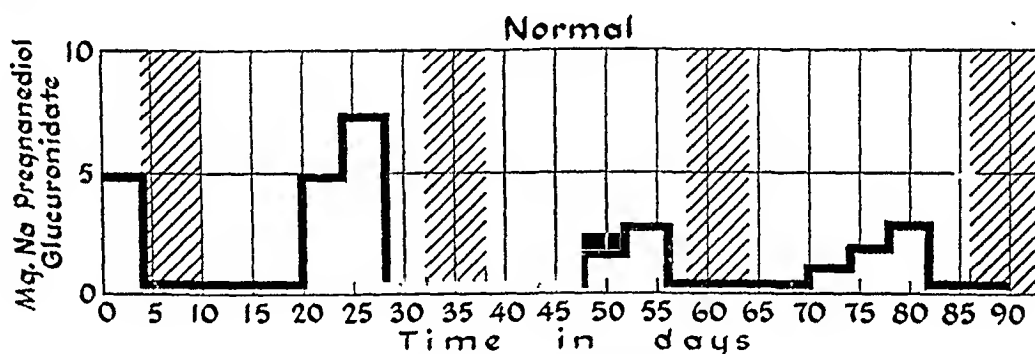


Fig. 1.—The normal excretion of pregnandiol in the urine during more than three cycles. The obliquely cross hatched lines represent the duration of menstrual bleeding. In a large number of studies no patient has been found who excreted proved pregnandiol during the course of a normal menstrual bleeding, although it has been found to be so excreted on occasion following the artificial administration of gonadotropins and progesterone.

### Case Histories

CASE 1.—Mrs. E. T. (U. H. No. 710797), a 39-year-old para 5-0-0-4. Prior to the birth of her last child three years ago, menses were normal in duration and quantity and recurred at intervals of four weeks. For the past three years the cycle had been from three to five weeks, the flow which was previously five days was now seven days and moderately profuse. A right oophorectomy was done nine years before present observation for unknown reasons. Hemoglobin on admission was 10.4 grams. Study showed a mild essential hypertension, but no other abnormality. Curettage on the fifth day of bleeding showed characteristic irregular shedding of the endometrium.

Excretion studies were carried out through the subsequent month, including the next menstrual period. This was short, possibly as a result of the previous curettage, but pregnandiol was excreted throughout the period of bleeding.

CASE 2.—Mrs. E. E. (U. H. No. 628741), a 42-year-old para 2-0-1-2. She had mild diabetes. Menses were normal until two years ago when the cycle began to vary from two to four weeks, and bleeding was profuse and prolonged.

### Conclusions

1. Irregular shedding of the endometrium is a specific form of functional uterine bleeding. It is an abnormality of true menstruation.

2. It is characterized clinically by prolonged and profuse menstrual bleeding, and histologically by retention over variable periods of time of abnormal amounts of endometrium which has functioned.

3. The endometrium shows abnormalities of the basic endometrial features of menstruation in various degrees of retardation of shrinking, shedding, involution of glands and stroma and healing.

4. Sodium pregnandiol glucuronidate is excreted in the urine during the time of the uterine bleeding. This is not seen in other conditions, and seems to be characteristic of irregular shedding of the endometrium.

5. Histologic diagnosis is essential, and requires timing of the curettage in relation to the expected duration of the bleeding.

6. Clinical experiences with 34 cases of irregular shedding are briefly summarized.

### Reference

McKelvey, J. L.: *Lancet* 42: 434, 1942.



struate or bleed in December, 1939. She began to bleed from the uterus on Jan. 15, 1940, and this continued to admission on Feb. 26, 1940. A curettage showed characteristic endometrial hyperplasia. Following this, menses became regular and apparently normal. This lasted to Feb. 21, 1941, when she bled for three weeks. She bled again from April 20 to May 3, and from May 25 to curettage on May 29 when endometrium showing characteristic irregular shedding was obtained.

Excretion studies were carried out over the following cycle. Pregnandiol was excreted in large quantity during the premenstrual phase. A portion of this was ruined due to technical difficulties. Pregnandiol was excreted again during the bleeding, and for a short time in the post menstrual period.

This is one of the patients who have been proved to pass from endometrial hyperplasia to irregular shedding, or vice versa.

CASE 4.—M. L. (U. H. No. 628263), a 39-year-old para 7-0-0-7. She had profuse vaginal bleeding following the birth of her last child in 1933 and was curetted three months post partum. After this her menses came at about four-week intervals, but were irregularly profuse and lasted for 10 to 14 days. Curettage was done on three occasions, but had no effect on the bleeding. The last of these was done on the ninth day of bleeding and showed an irregular shedding. During the excretion studies illustrated, she bled for sixteen days.

Excretion studies showed high levels of pregnandiol excreted during most of the bleeding. It is interesting to note that it reappeared in the urine five days after cessation of bleeding which was, however, twenty-one days after the onset of the bleeding.

On February 25, a hysterectomy and biliary salpingo-oophorectomy were done. The right ovary contained a corpus luteum in full vascularization stage. The endometrium was well proliferated and showed evidence of early secretion phase change. Following this, pregnandiol excretion ceased.

CASE 5.—Mrs. E. J. (U. H. No. 705174), a 22-year-old nullipara. Menses began at 14 years of age, and recurred at four-week intervals. At time of admission they lasted 7 to 10 days and were very profuse. Admission hemoglobin was 8.65 grams. Curettage was done on the thirteenth day of bleeding and showed almost complete regeneration of the endometrium. She was admitted again at the following midinterval for endocrine studies which are illustrated. Pregnandiol was excreted during the bleeding phase and immediately thereafter. Curettage was done on the fifth day of bleeding, and only spotting occurred thereafter for nine days.

CASE 6.—Mrs. L. A. (U. H. No. 714211), a 35-year-old para 5-0-1-5. Menses were normal until two years previous. The cycle then changed from 28 to 23 to 25 days, and the duration of the flow from 5 to 6 up to 14 days and became more profuse. She was curetted on the sixth day of bleeding, and the characteristic endometrium of irregular shedding was obtained.

Excretion studies showed the appearance of pregnandiol in the urine on the fourteenth day of the cycle. This disappeared just before the onset of the next bleeding, which lasted only six days. It is possible that this patient is one of those who for some unknown reason are cured of irregular shedding of the endometrium by curettage.

menstrual cycle. While not scientifically accurate, this procedure is used in keeping with time-honored custom. The period of flow is actually the termination of the cycle, rather than the beginning of a new cycle.

The 100 patients were operated upon on various days of the cycle (Fig. 1). Days 3 and 27 were the only two days on which no patient was operated upon, and consequently no representative tissues are available. Fifty-three patients were operated upon on or after the fifteenth day of the cycle. All except four of these patients had ovulated. These four will be discussed later.

In Fig. 1 those blocks that contain numbers indicate that the patient had ovulated, and the number indicates the estimated age of the corpus luteum in each instance as determined histologically. The blocks are arranged on the chart in accordance with the day of the cycle on which the patient was operated upon.

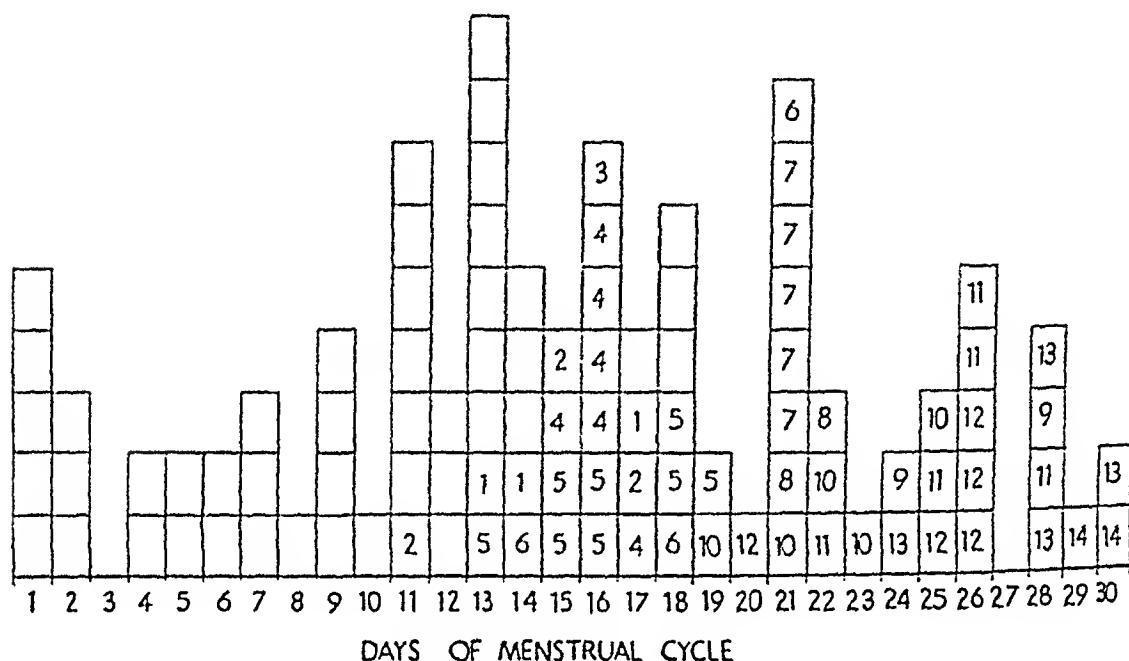


Fig. 1.—Those blocks that contain numbers indicate that the patient had ovulated and the number indicates the estimated age of the corpus luteum in each instance as determined histologically. The blocks are arranged on the chart in accordance with the day of the cycle on which the patient was operated upon.

A breakdown of this chart shows that 54 of the 100 patients had ovulated during the present cycle studied. The data of these 54 patients are arranged in Fig. 2. Each block represents one patient. The block is placed on the chart according to the day upon which it is estimated that ovulation occurred. This day is arrived at by subtracting the estimated age of the corpus luteum from the day of the cycle upon which the patient was operated upon. The upper number in each block represents the age of the corpus luteum as estimated histologically. The lower number indicates the day of the cycle upon which the patient was operated upon.

The range of time of ovulation is from the eighth through the nineteenth days of the cycle. There was only one patient, however, who ovulated after the seventeenth day of the cycle. There seems more tendency to ovulate early in the cycle rather than late as there were more who ovulated on days 8, 9, 10, and 11 than on days 16, 17, 18, and 19.

## THE TIME OF OVULATION\*†

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THE time of ovulation in the human female has both clinical and scientific significance. Human fertility studies can be complete only with this knowledge. A thorough understanding of the human menstrual cycle including histologic and physiologic aspects is dependent upon a cognizance of the time of ovulation. The estimation of age of very young embryos such as those studied in this laboratory by Brewer and Fitzgerald<sup>1</sup> and those reported by Hertig and Rock<sup>2</sup> is at the present time more accurately made if the time of ovulation is known.

For many years determination of ovulation time has been attempted by estimating the age of corpora lutea histologically. The results, as most authors state, have been quite inaccurate due to a lack of knowledge concerning the histologic and cytologic characteristics of the corpus luteum in all phases of its life. Recently Corner,<sup>3</sup> in collaboration with Hartman and Bartelmez, stated that in the Rhesus monkey accurate age determination of the corpora lutea could be made, and that human material could also be correctly interpreted. We are in accord with this latter statement, since our experience gained in fifteen years of study of human corpora leads us to believe that reasonably accurate age calculations can be made by histologic and cytologic studies of corpora lutea.<sup>4</sup> A range of two days in calculated age is considered reasonable. It is with this background that data concerning the time of human ovulation based on microscopic determination of age of corpora lutea are presented here.

### Material

The material comprising this report was obtained from 100 women who were in active menstrual life. All had menstrual cycles within the limits established for normal. In most some pelvic pathology was present, but in no instance had it disturbed the menstrual rhythm. No effort was made to operate upon these patients at a given time in the menstrual cycle, since it is felt that failure of ovulation to occur by the expected time is as important as the fact that ovulation did occur. These patients were not selected in any way. The material consists of surgical specimens of the ovary, ovaries, or resected portions of ovaries and endometrium.

Exact menstrual dates and histories are of prime importance in such a study as this in order to establish accurate time relationships. Realization of this, in addition to the fact that the collection of material was planned and methods organized prior to starting this project, afforded the opportunity to get exact dates. In addition to the usual hospital history taken with stress placed on accurate menstrual data, a laboratory assistant made separate records by personally interviewing each patient and establishing accurate calendar dates. As a result we believe that errors are at a minimum.

In all instances the days of the menstrual cycle are counted from the last period of menstrual flow, day one of the bleeding period being the first day of

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†Aided by grants from C. V. Essroger and the Billings Medical Club of Chicago.

who had not ovulated. These patients, with one exception, would undoubtedly have ovulated soon as determined by the presence of mature follicles in the ovaries. The one exception was a patient 48 years of age who was operated upon on day 14. Both ovaries were available for microscopic study, but in neither was there a mature follicle or a corpus luteum of the present cycle. Two degenerating corpora lutea of the previous cycle were present. The degree of development of the endometrium was consistent with these findings (Fig. 3).



Fig. 3.—Photomicrograph of endometrium showing slight stimulation. Patient operated upon on day 14. There were no mature follicles or corpus luteum of present cycle in the ovaries.

The usual length of the cycles in this patient was twenty-four to twenty-five days. From this it would seem probable that ovulation, if it was going to occur, would have occurred by the day of operation (day 14). The absence of a mature follicle suggests that either this patient was not going to ovulate during this cycle, that a period of amenorrhea was ensuing, or that if uterine bleeding did occur this might represent an anovulatory cycle. This is the only instance in the entire group of 100 in which failure of ovulation was strongly indicated.

The ovaries of the four patients who had not ovulated by the seventeenth and eighteenth days of the cycle contained mature follicles (Fig. 4), which suggests that ovulation would have occurred very shortly. The interpretation is that ovulation in each of these patients would have occurred by the nineteenth day, which is the upper limit of the range as indicated in Fig. 2.

The greatest number ovulated on days 12, 13, 14, and 15, with the highest peak on day 14. Of the 54 patients who ovulated, 36, or more than half, ovulated during this four-day period.

Five patients ovulated early in the cycle (eighth and ninth days). Their menstrual cycles were not short as one might expect but varied from twenty-eight to thirty days in length.

One of these patients had in the ovary a young corpus luteum estimated to be two days of age. The endometrium was developed to a degree consistent with this age of corpus luteum. If the postovulatory phase of the cycle is of a fairly standard length (fourteen or fifteen days), as most authors believe, this menstrual cycle in all probability would have been of shorter length than usual as indicated by the history.

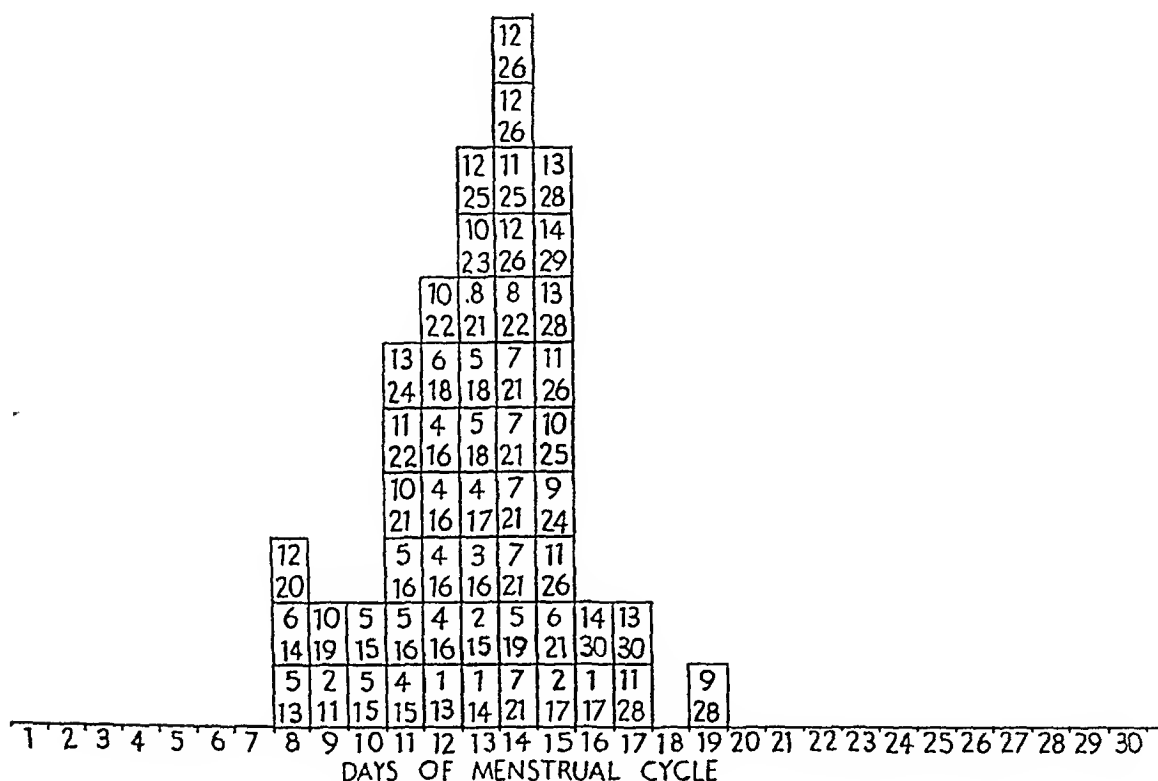


Fig. 2.—Each block represents one patient. The block is placed on the chart according to the day upon which it is estimated that ovulation occurred. The upper number in each block represents the age of the corpus luteum as estimated histologically. The lower number indicates the day of the cycle upon which the patient was operated.

The one patient who ovulated on day 19 was operated upon on the twenty-eighth day of her cycle, and, although her cycles were usually 28 days in length, was not yet ready to menstruate as determined by a study of the endometrium and the corpus luteum. The corpus luteum was estimated to be approximately nine days of age. This cycle was longer than customary.

One patient who had short cycles (twenty-one to twenty-three days) was operated upon on day 15. The corpus luteum was estimated to be five days of age. Thus ovulation occurred on the tenth day, relatively early in the cycle.

Forty-six patients had not ovulated during the present cycle under study (Fig. 1). All of these except four were operated upon between the first and fourteenth days, inclusive. Many of these were operated upon so early in the cycle that ovulation would not be expected to have occurred. However, there were seven patients operated on day 13, and three patients operated on day 14

normal human embryos. Their experience in the calculation of ages of young embryos, aided by exact menstrual histories recorded for their patients, has added an additional valuable factor in determining the time of ovulation. Their evidence indicates that ovulation takes place about fourteen days before the first day of the next expected menstrual period. In patients with 26- to 30-day cycles, ovulation would thus occur at or near the mid-cycle, that is, the twelfth to the sixteenth day. This work is the most adequate as far as the human is concerned.

Allen, Pratt, Newell, and Bland<sup>6</sup> recovered unfertilized ova in the human being, and, from a study of these ova and the associated corpora lutea, concluded that ovulation occurred approximately on day 14 of a 28-day cycle.

Hartman<sup>7</sup> was able to discern the time of ovulation quite accurately in the Rhesus monkey by rectal palpation. His data indicate that ovulation takes place from the ninth to the eighteenth days, with the bulk from the twelfth to the fifteenth days of the cycle.

Corner,<sup>8</sup> in collaboration with Hartman and Bartelmez, estimated the ages of corpora lutea of the Rhesus monkey by histologic and cytologic methods. Some of the specimens were obtained from fertile cycles and the determined ages of the young embryos were used in calculating the time of ovulation. The conclusion reached was that ovulation usually took place approximately fourteen to fifteen days before the onset of the next expected menstrual period. The published chart indicates a range of time of ovulation from the eighth to the twenty-first days of the cycle.

Grnelieh, Morris, and Black<sup>8</sup> combined the determination of ages of corpora lutea with a study of the body temperature fluctuations in the human female during the menstrual cycle. They offer evidence that a temperature fluctuation occurs at the time of ovulation and believe that ovulatory and anovulatory cycles can be differentiated by basal rectal temperature studies. The determined time of ovulation was during the midcycle. Zuck,<sup>9</sup> Rubenstein,<sup>10</sup> and others have offered evidence supporting this view. Davis<sup>11</sup> recently has shown that oral temperature records are as reliable as rectal temperatures.

Lamar, Shettles, and Delfs<sup>12</sup> found that ovulation took place from the ninth through the nineteenth days of the cycle. This was based on the observation that cervical mucus is more abundant, contains fewer leucocytes, and is temporarily permeable to spermatozoa at the time of ovulation.

Papanicolaou,<sup>13</sup> by the vaginal smear method, determined the time of ovulation within two or three days in some but not all women. He found that ovulation occurred most often on days 11, 12, and 13, with a range from day 7 to day 17.

Studies of sodium pregnandiol glycuronidate excretion in the urine (Venning and Browne<sup>14</sup>) similarly indicate that ovulation takes place during the midcycle.

This brief compilation of some of the data concerning the time of ovulation demonstrates that ovulation usually takes place during the midcycle, with a range from the eighth to the nineteenth day in patients with 26- to 30-day

Degenerating corpora lutea of the previous cycle were demonstrated in the ovaries of the 46 patients who had not as yet ovulated during the present cycle. The follicular and endometrial development in these patients, with the one exception noted above, was consistent with the stage of the cycle in which the tissues were removed.

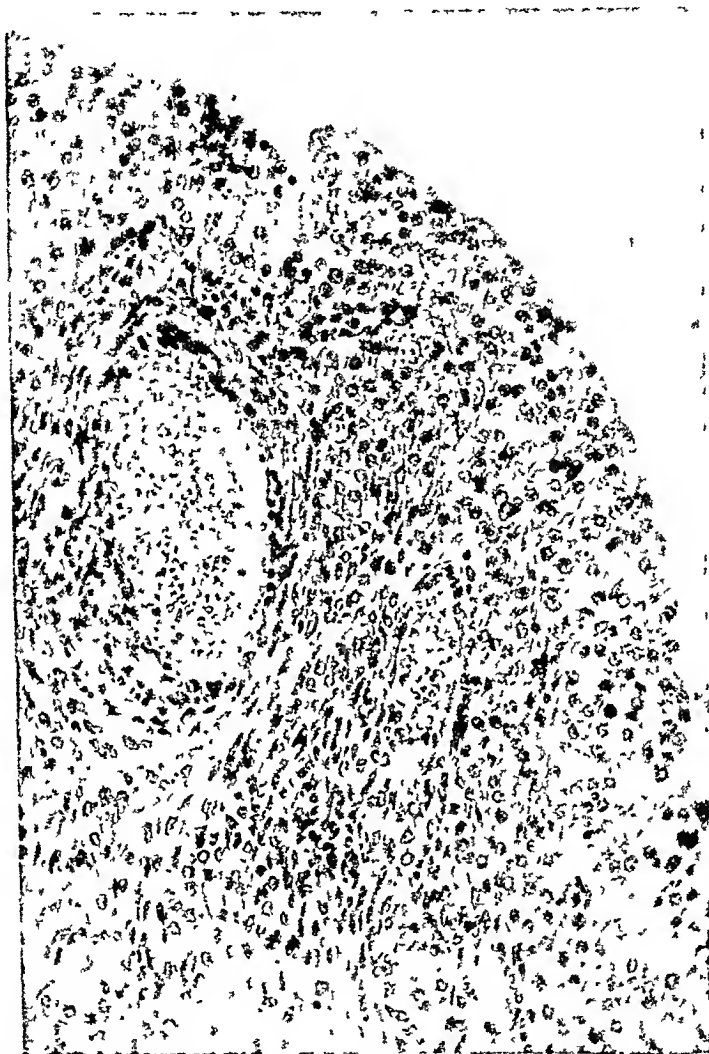


Fig. 4.—Photomicrograph of mature follicle in ovary of patient operated upon on day 18. (X198.)

### Discussion

It is impossible at this time to demonstrate the actual phenomenon of ovulation in the human being. Therefore, it is necessary to obtain data by indirect evidence. The acquisition of such data requires considerable time and confirmation before the facts can be considered established. Studies of the time of ovulation made from various standpoints and published in numerous reports indicate quite consistent findings. These are so consistent that the evidence is now considered as fact.

Rock and Hertig<sup>5</sup> accumulated important information by a study of the endometrial histology, histology of the follicle or the recent corpus luteum, the cytology of the unfertilized ovum, and in many instances the age of very young,

when it falls to the preovulatory level. In the event pregnancy ensues, no premenstrual drop occurs, thereby providing early evidence of a gestation.

In over 500 records thus obtained during the last two years, the rise in basal body temperature occurred most often between days 11 and 15 in the usual 27- to 31-day cycle. Regardless of the length of the cycle, the ovulatory rise occurs most frequently about fourteen days prior to the onset of the next menstrual period. This simple clinical procedure confirms these data presented by Dr. Brewer and provides an important addition to our gynecologic and endocrinal studies.

Several theories have been suggested as causes for the temperature rise. The following unpublished experiment provides a satisfactory explanation. During the past six months we have taken several groups of women who have not ovulated for various reasons, such as primary amenorrhea or the surgical removal of the ovaries. After a basal temperature record was obtained for a month, the patients were placed on estrogens for several weeks. No rise in temperature occurred. The estrogens were continued, but 10 mg. of progesterone was administered intramuscularly daily. The temperature rose, reached a plateau, and remained elevated as long as progesterone was administered. When progesterone was discontinued, the temperature returned to the base line within thirty-six hours. Thus, we have provided proof that the rise in temperature during the last two weeks of the cycle is due to progesterone elaborated by the corpus luteum.

DR. H. S. GUTERMAN.—I should like to bring to your attention some observations we have been making at Michael Reese Hospital in the last six years. We have been conducting a study in functional sterility, employing the technique of basal body temperature and vaginal smear for the detection of ovulation, as originally described by Rubenstein. In a recent summary of the work on 67 patients, we noted that 18 had become pregnant. We are able to correlate the basal body temperature and vaginal smear as follows: In those cycles in which pregnancy occurred, the basal body temperature rise indicating ovulation occurred in 17 out of 18 cases; the vaginal smear indicated ovulation according to the criteria set down by Rubenstein, in 6 out of the 18 cases. It seems that basal body temperature is a reliable aid in detecting ovulation. The time of ovulation apparently falls within the limits described by Dr. Brewer. In the total series of 450 cycles which we analyzed, ovulation was indicated in 75 per cent by basal body temperature. Vaginal smear indicated ovulation in about 50 per cent of the cycles. Basal body temperature taken orally or rectally constitutes a very simple technique. The vaginal smear indicates estrogenic activity primarily.

DR. G. W. BARTELMEZ, Atlanta, Ga.—Among 30 animals in the monkey colony in Atlanta during a single breeding season, we found one in which ovulation did not occur until well along in the third week, and four during the fifth week of a cycle; that is to say, four to five weeks after the beginning of the last period. We were using Hartmann's rectal palpation method so we could say with certainty that in these cases the ovaries had been inactive for a period of two to three weeks. When palpation is done every day or even every other day, you can be fairly certain of growth of the Graafian follicle. In addition, the monkey in prime condition will show the sex skin pale during the flow, and then brightening up sooner or later afterward. The brightening clearly indicates increased ovarian activity. I am inclined to regard these cases as evidence of a postmenstrual period of inactivity, and I do not see why a similar condition should not occur in the human being. That would account for reports in the literature of ovulation on the twenty-eighth to thirtieth day of the "cycle." Actually, it means nothing in regard to the fundamental relationships between the ovaries and the endometrium. It simply means a period of inactivity following a menstrual period.

I recently had the opportunity to read an article by an investigator in Berlin who studied the reproductive system of more than 100 women killed by the Nazis. This author (Stieve) maintains that ovulation may occur at any time of the cycle, or there may be two ovulations in the single cycle. The relationship between the ovaries and uterus is of the vaguest type, according to this man. Nevertheless, some of his data fit in with the notion that we had gained from a study on monkeys: that there may be an inactive period following menstruation, and that ovulation may occur very late. Nevertheless, a perfectly normal corpus luteum develops.



cycles. The study presented here demonstrated a similar midcycle peak and a similar range of time of ovulation.

The consistency of the various reports, many of which are based on determination of age of corpora lutea, indicate that it is possible to estimate the age of corpora lutea reasonably accurately by histologic and cytologic methods.

### Conclusion

1. Ovulation in the human female is shown to take place between the eighth and nineteenth days of the cycle in 100 patients with normal menstrual cycles presented here. Ovulation in these patients occurred most frequently on days 12, 13, 14, and 15.

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### Discussion

DR. M. EDWARD DAVIS.—Dr. Brewer has provided additional concrete evidence concerning the time of ovulation in the human female. His excellent study of corpora lutea has provided in addition a basis for evaluating their age from histologic appearances. Direct and indirect evidence amply confirm the accepted idea that ovulation occurs during the mid-interval of the normal cycle of average length, most often during days 12 to 15, more rarely earlier or later. Like all biologic phenomena dependent on a complicated hormonal interrelationship, the time of ovulation will vary widely.

Clinically, it is of the utmost importance to determine the period of ovulation. The information obtained by endometrial biopsies and pregnandiol excretion in the urine provide indirect information only. Furthermore, these data concern the ovulation that has occurred, and thus too late to be useful in gynecologic therapy. Body basal temperature offers a simple and efficient clinical means to determine the ovulatory period.

During the last two years we have instructed all of our patients at the Lying-In Hospital in whom it was important to know the time of ovulation to plot a careful basal temperature graph. The simplest way to obtain an instructive record is to ask the patient to take her temperature, orally, immediately on arising each morning and to record it promptly on the specially prepared graph. These data will be more valuable if she is asked to record coitus, special medication, and unusual incidents.

In three out of four women a properly prepared body basal temperature graph will indicate the ovulatory period. In the fourth patient, irregular activity, excitement, and extraneous factors may fail to provide an informative curve. With the onset of menstruation the body temperature is low and may continue to drop slightly until the end of the bleeding phase. The body temperature remains at about the same level until the period of ovulation when it rises abruptly during twenty-four to thirty-six hours. Having reached a plateau it will remain at that level until twenty-four to thirty-six hours preceding the next menses,

Three methods of vitamin C assay were used. (1) Whole blood determinations were made by the method of Roe and Kuether<sup>6</sup>. This method was also used for many of the placental studies, grinding weighed portions of tissue with sand in measured amounts of 8 per cent trichloroacetic acid and assaying the fluid. (2) The technique of Mindlin and Butler<sup>7</sup> was employed to check the placental analysis. Both this and the Roe and Kuether method had to be adjusted with respect to amounts of tissue and extracting solution used since the vitamin C content of placenta proved to be so much higher than that of blood that proportionately smaller amounts of placenta and larger amounts of solution were necessary to bring the readings of the photoelectric colorimeter within the optimum range. (3) The direct titration method of Bessey and King<sup>8</sup> was also employed as a further check on the placental levels. This was modified only by standardizing the 2-6 dichlorophenol indophenol daily against a fresh solution of crystalline vitamin C rather than against lemon juice.

Carotene and vitamin A levels were determined on both blood and placenta by the technique of Dann and Evelyn as modified by Kimble.<sup>9</sup> The placental tissue was ground with sand in the 95 per cent alcohol using 5 Gm. of tissue where the method calls for 5 c.c. of blood. The vitamin B analyses were made by the technique of Melnick-Field-Emmett.<sup>10</sup>

*Results.*—Blood levels. The observation that the fetal vitamin C level is higher than the maternal was found to apply to whole blood determinations. Maternal venous whole blood levels ranged from 0.29 mg. per cent to 1.8 mg. per cent. Fetal cord blood levels ranged from 1.2 mg. per cent to 2.48 mg. per cent, and were always greater than the corresponding maternal blood. No constant ratio between the two blood levels could be determined.

*Placental Levels.*—The difficulty with placental analyses of ascorbic acid rests with the specificity of the reaction. There are present in the tissue reducing substances which have the ability to interfere with a method based entirely on the reduction of 2-6 dichlorophenol indophenol (techniques 2 and 3 above), as well as substances which would give a false color reaction with 2-4 dinitrophenylhydrazine and sulfuric acid (technique 1 above). Since the amounts of these elements which might yield nonspecific changes are not measurable, a potential error is introduced which must be guarded against. It was for this reason that multiple methods of assay were used, and with the dichlorophenol indophenol techniques only rapid fading (20 seconds) of the dye was read. Nevertheless, achieving complete agreement between the results obtained was difficult, and after comparative analyses performed on twelve placentas each run in varying dilutions, it was concluded that in our hands the direct titration method produced the least error. The dinitrophenylhydrazine technique,<sup>6</sup> which was the most satisfactory for whole blood, produced the greatest error in the form of elevated readings.

The placental levels expressed in milligrams per 100 Gm. of tissue ranged from 4.7 to 21.0, with a mean reading of 9.4. Only term or near term placentas are considered here, since in the premature delivery an abnormality of local tissue vitamin C concentration might have been a contributory factor in the prematurity. In each of the 84 cases, the placental level was considerably higher than either of the blood levels involved, ranging (in milligrams per 100 Gm. placenta) from 3 to 10 times the fetal blood content (in milligrams per 100 c.c.). No constant factor could be determined relating the placental ascorbic acid to either the maternal or the fetal whole blood levels, and this statement applies equally to the placental level expressed in milligrams per cent and to the total placental content.

# PLACENTAL METABOLISM OF VITAMIN C

## I. Normal Placental Content

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THE evidence directly relating vitamin C with the process of reproduction is constantly accumulating. The recent papers of Lardy, Casida and Phillips,<sup>1</sup> as well as of Korenchevsky and Hall<sup>2</sup> summarize much of this work. With respect to the fetal-maternal relationship, McDevitt and co-workers<sup>3</sup> and Lund and Kimble<sup>4</sup> have postulated a selective retention of vitamin C by the placenta.

The extensive study of Lund and Kimble<sup>4</sup> bears consideration. They confirmed the observation that in a fasting or near-fasting state the fetal ascorbic acid level is always greater than the maternal. Subsequent to the administration of vitamin C, both the fetal and maternal plasma levels rise, followed in a few hours by a drop in the maternal level, while the fetal plasma ascorbic acid remains higher. Their tentative hypothesis, that the placenta permits free maternal-fetal passage of ascorbic acid, while limiting fetal-maternal passage, must be examined closely in view of Needham's observation that electrolytes of low molecular weight pass freely and equally in both directions across the placental barrier.<sup>5</sup>

These significant observations led us to undertake a study of the placental metabolism of vitamin C. The present report has the purpose of (a) extending the observations of the maternal-fetal plasma ascorbic acid relationship to whole blood, (b) correlating these levels with placental assays of vitamin C, (c) ruling out the possibility of ascorbic acid synthesis by the placenta, and (d) determining whether or not such selective retention is a nonspecific nutritional function of the placenta which applies to all vitamins.

## Materials and Methods

Over 80 placentas have been analyzed in the course of this work. Preliminary assays were made to determine the loss incident to storage of the tissue or to delay in carrying out the extraction, and the following routine established: as soon as the placenta was delivered, inspected for completeness, and weighed and measured it was taken to the laboratory. If the assay could not be undertaken within a few minutes, the placenta was wrapped to exclude light and air. If more than an hour was to elapse, a weighed portion was ground in 8 per cent trichloroacetic acid and an aliquot of the solution was drawn off for ice-box storage in a tightly stoppered container. Cord blood was usually collected prior to delivery of the placenta, and maternal blood by venipuncture at the same time. Samples for uterine wall analysis were obtained at cesarean section and studied immediately.

niques previously indicated. In each of these sets of analyses the results were expressed in micrograms per 100 Gm. of placenta for comparison with micrograms per 100 c.c. of blood.\*

**Carotene.**—The highest levels of carotene were found to occur in the mother's blood, the lowest in the fetal blood, and (with the exception of a single case) the placental level fell in between the two. There is apparently a step-like gradient of carotene with declining amounts from mother to placenta to fetus.

**Vitamin A.**—Vitamin A was also found to be consistently higher in the maternal than in the fetal blood. In three of the five cases analyzed, however, the placental level was lower than the fetal blood level, whereas in the other two cases the level in the placenta was slightly higher than in the fetal blood.

**Thiamin.**—With thiamin the blood levels were approximately equal between mother and fetus, the cord blood in each instance being slightly lower. The placental levels were significantly lower, being about one-half or less of the fetal blood levels.

From these results it can be readily seen that the consistent relationship displayed by vitamin C (i.e., with the fetal blood level higher than the maternal and the placental concentration considerably higher than in either of the bloods) is not shown by either of the other vitamins studied. It can be concluded from this that the observations with respect to ascorbic acid do not represent a non-specific nutritional function of the placenta, but indicate a relationship peculiar to vitamin C itself.

While placental levels are not in general available, it is of interest to compare these findings with other known maternal-fetal relationships.<sup>12</sup> Urea, uric acid, creatine, and creatinine have equal levels on both sides of the placental barrier, and presumably pass it by simple osmosis. Glucose, despite its structural similarity to cevitamic acid, has just the opposite relationship, being higher in the maternal blood than in the fetal. On the other hand, the amino acids and the nonprotein nitrogen levels, like vitamin C, are reported as being higher in the fetal blood than in the maternal.

### Conclusions

1. The observation previously made that the ascorbic acid level in the fetal plasma is always higher than that in the maternal plasma has been found to apply to whole blood.

2. Simultaneous assays of the placenta for vitamin C have indicated that it has an exceedingly high level in comparison with either the maternal or the fetal blood. The placental levels were also higher than those found in uterine muscle or umbilical cord.

3. In vitro experiments with placental slices give no evidence to indicate that the human placenta can synthesize ascorbic acid.

4. Comparable assays of carotene, vitamin A, and thiamin in the placenta, the maternal and fetal bloods give results totally different from those obtained with vitamin C. The relationship observed with ascorbic acid is apparently peculiar to that substance, and is not representative of the placental metabolism of all vitamins.

\*The range of values obtained was as follows: Maternal blood: carotene, 70 to 250; Vitamin A, 56 to 185; thiamin, 2 to 4. Fetal blood: carotene, 13 to 38; vitamin A, 25 to 178; thiamin, 1.4 to 3. Placenta: carotene, 22 to 132; vitamin A, 32 to 138; thiamin, 0.5 to 2.

*Local tissues:* Specimens of uterine wall removed at cesarean section were examined in five cases, coincidentally with placental assay from the same patient. The uterine sections, like the placental specimens, were removed to include the whole wall in about equal thickness. These levels, in milligrams per cent, ranged from 2.4 to 9.1. They were in each case approximately one-third the placental level, although in all cases they exceeded the maternal whole blood level. Umbilical cord tissue levels (four cases) were low to the point of being negligible (average 0.06 mg. per cent), and were a small although not constant fraction of the fetal blood contents.

It becomes evident from the above results that the placental vitamin C level is high, in relation both to the adjacent tissues and to the associated bloods. There are two possible explanations for this relationship. The first, that of selective retention of ascorbic acid by the placenta, has been suggested by Lund and Kimble.<sup>4</sup> There is also the possibility, however, that the placenta might be a site of vitamin C synthesis.

That this vitamin is synthesized in animal tissues is well known, and Smythe and King<sup>11</sup> have made in vitro studies of such synthesis in tissues from the albino rat. While such synthesis is unknown in most human tissues, in vitro studies of human placental tissue are not available. In view of the fact that the placenta is rich in related substances which could serve as possible precursors, and in consideration of the relatively high vitamin C levels found, the possibility of placental vitamin C synthesis was checked by in vitro determinations.

*Technique and Results.*—The method of Smythe and King<sup>11</sup> was modified for our purposes. A 1 Gm. slice of tissue was incubated at 37° C. in a stoppered flask containing 10 c.c. of media and filled with 5 per cent CO<sub>2</sub> and 95 per cent nitrogen. The following media and substrates were used: Ringer's solution, Ringer's solution and human plasma in equal amounts, Ringer's-Plasma mixture containing 2.5 per cent glucose, and Ringer's-Plasma containing 2.5 per cent glucuronic acid. In half of the determinations the placental tissue was washed with normal saline as a preliminary to remove the ascorbic acid present, in the other cases the tissue was placed in the solution for incubating directly after cutting.

At hourly intervals for four hours, and then at twelve-hour intervals for thirty-six hours, 1 c.c. lots of the media were withdrawn and titrated for ascorbic acid content, the flask refilled with the gas, and the incubation continued. Control determinations were made on the original C content of the placenta as well as on the four solutions used as media. In no case was there any evidence of an increase in vitamin C level of the withdrawn fluid, and a final assay of the placental tissue itself showed no increase in ascorbic acid. In other words, the possibility that the placenta synthesizes the vitamin as do animal tissues can apparently be ruled out.

These results would tend to substantiate the postulate that the differential between the maternal and fetal blood levels results from a selective retention of ascorbic acid at the placental barrier. The postulate that fetal blood or tissues themselves have the power to "fix" ascorbic acid would not, if true, account for the proportionately large placental levels. The question immediately arises as to whether or not this retention and storage of C is a nonspecific nutritional function of the placenta which applies equally to all vitamins. Accordingly, similar simultaneous analyses of placental tissue, the maternal and the fetal bloods were run for carotene, vitamin A and thiamin, using the tech-

# THE POSSIBLE ETIOLOGIC SIGNIFICANCE OF THROMBOSIS OF A PLACENTAL VEIN ON THE MECHANISM OF PLACENTAL INFARCTION AND ASSOCIATED TOXEMIA OF PREGNANCY

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THE following case is deemed worthy of reporting on account of the visible evidence of recent thrombosis of a placental vein, acute infarction of the dependent placental tissue, and the development of acute toxemia, indicating a probable relationship of the phenomena.

Mrs. K., aged 28 years, gravida i, para 0, was due to be confined Nov. 16, 1939. Pregnancy had progressed normally until the evening of October 20, when there was a painless sudden discharge of bright red blood sufficient to soil her clothes and the toilet. The blood pressure was 110/78, and the urine showed no albumin. Examination at the hospital on October 21 showed the fetal head easily palpable through the lower uterine segment and no bleeding from the examination. A low-lying placenta was suspected, but expectant treatment followed.

On November 9 she showed a gain of  $5\frac{1}{2}$  pounds for the preceding two weeks, slight edema, and a rise in diastolic blood pressure from 60 up to 80, but no albuminuria.

On November 22, the blood pressure was 120/90 and the urine showed a light cloud of albumin, but there was no further increase in edema and no headache. Induction of labor was advised and on November 25, following administration of castor oil and 0.65 Gm. (10 grains) of quinine, labor began at 12:30 A.M. on November 26, progressed rapidly, and normal delivery occurred at 8:20 A.M., the baby being in good condition. The site of the opening in the membrane near the margin of the placenta indicated low implantation.

A catheterized specimen of urine was concentrated, highly colored, and boiled almost solid with heat and dilute acetic acid. The sediment showed numerous coarsely and finely granular casts. Retinal examination on the second day following delivery showed many sharp and spindle-shaped arterial spasms but a normal A-V ratio, no increased light reflex, and no hemorrhages. On Jan. 11, 1940, the blood pressure was still slightly elevated, 135/85, and the urine showed a faint trace of albumin.

The placenta showed the appearance seen in Fig. 1. A thrombosed vein was seen on the fetal surface, extending centrally to the cord from the point of origin near the periphery of the placenta. A broad area of acute infarction was present where the thrombosed vein emerged from the fetal surface of the placenta and was plainly demarcated from the uninvolved portion of the placenta. The area of infarction on the maternal surface of the placenta showed a deep circular indentation about 3 cm. by 4 cm., filled with firm black clot (Fig. 2).

Examination of the placenta after fixation in 10 per cent formalin for several weeks showed massive acute infarction of the "E" type, seen as dark areas throughout the strip shown in Fig. 3, and also a "C" type of infarction lining the indented area, as shown by the middle arrow.

Microscopically, the "E" type of infarction showed congestion and engorgement of the villous capillaries and early necrosis of the stroma, Lang-

The author wishes to express his sincere appreciation to Miss Eloise White for her technical assistance.

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*(Part II of this article, dealing with Histochemical Analysis, will be included in the next issue of the JOURNAL.)*



han's, and syncytial layers of the villi. The intervillous spaces showed no thrombosis and were freely open and communicating. The "C" type of infarction showed partial thrombosis of the intervillous spaces but not sufficient to completely block intervillous circulation. The villi showed a slight hyalinized stage of degeneration, which is slower and characterized by very mild, if any, toxemia.

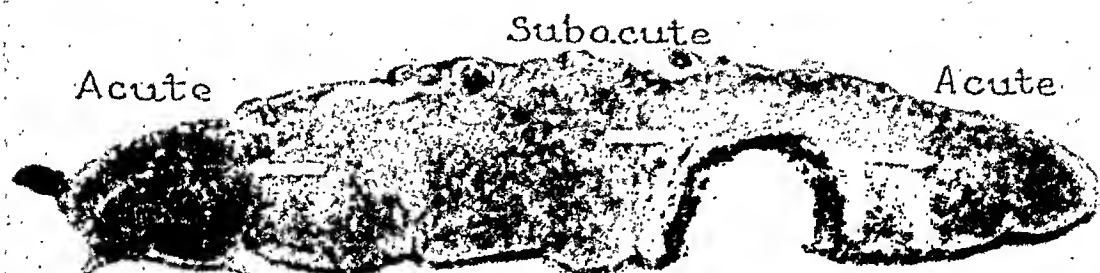


FIG. 3.—Placental strip cut through the areas of infarction showing subacute infarct of the "C" type, lining the indentation (central arrow) and dark areas of acute infarction of the "E" type on either side.



FIG. 4.—Microscopic appearance of thrombosed vein on the fetal surface of the placenta.

The thrombosed vessel was recognized to be a vein, both microscopically and by the fact that the artery in the affected area crossed over the vein in characteristic manner. Microscopically, it presented the appearance shown in Fig. 4. The process extended to the cord, but the latter presented nothing unusual in appearance.



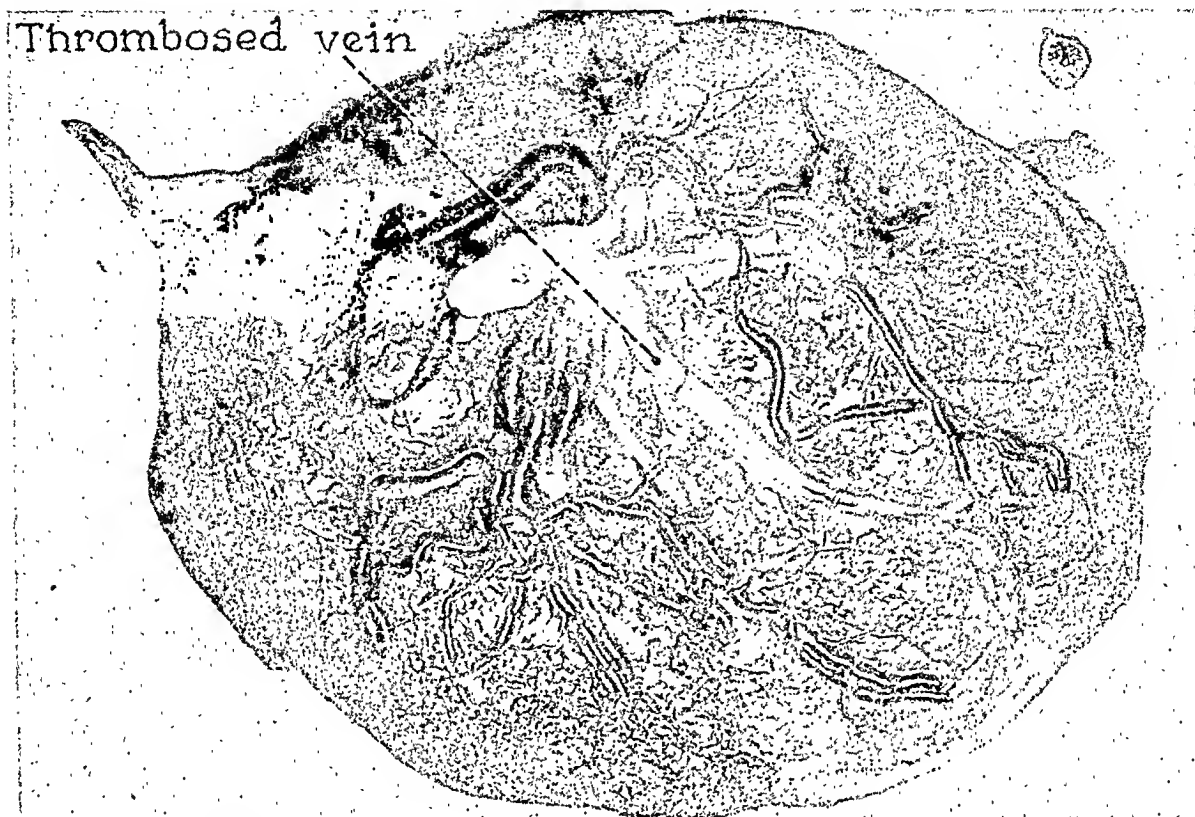


Fig. 1.—Placenta from case of Mrs. K, showing yellow thrombosed vein, arising from the area of acute infarction on the fetal surface of the placenta.

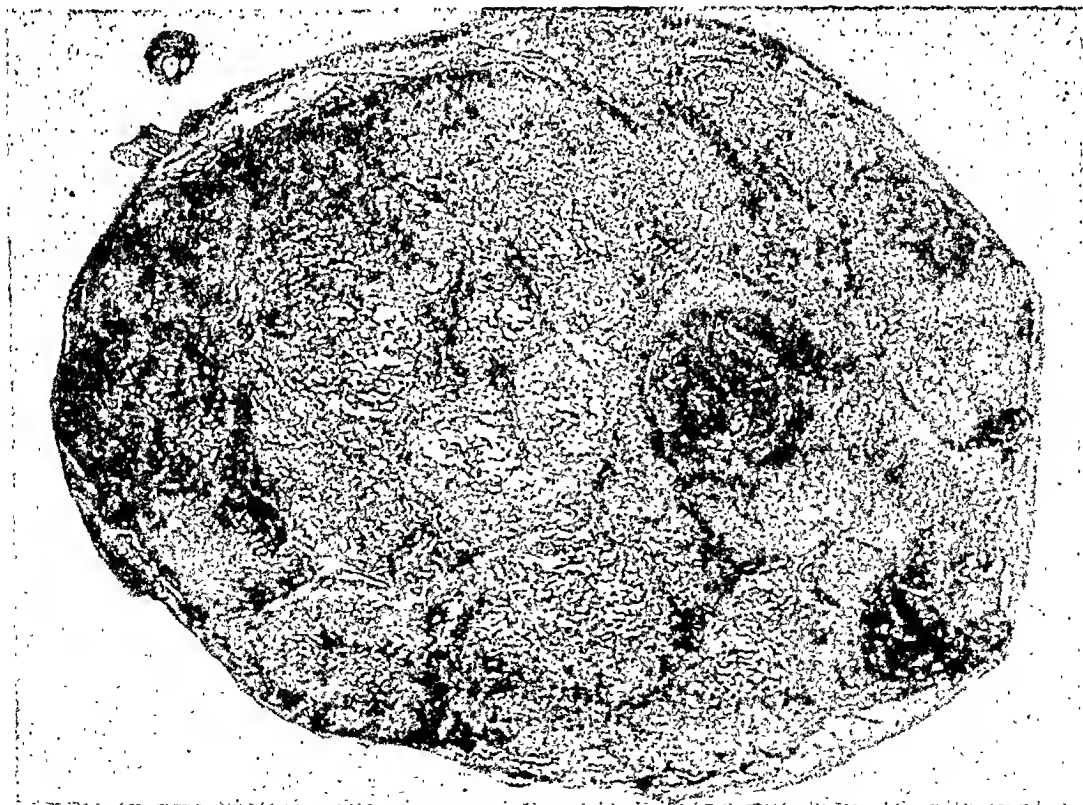


Fig. 2.—Maternal surface of the placenta, showing firm clot indenting placenta in the area of acute infarction.

down through a series of oxidation-reduction reactions to guanidine.<sup>10</sup> Guanidine is not only highly toxic, but is capable of producing convulsive seizures.<sup>11</sup>

The fact that toxic products of placental autolysis such as peptone histamine and guanidine are difficult to demonstrate in the maternal blood does not constitute a valid objection to this explanation of eclampsia. A toxin such as snake venom may not be demonstrated in the blood, but nevertheless produces a fatal effect through affinity for nerve tissue. The investigations of Major<sup>12</sup> Minot and Cutler<sup>13</sup> Andes and co-workers,<sup>14</sup> and Titus<sup>11</sup> indicate that hyperguanidinemia does occur in pre-eclampsia, notwithstanding the fact that the cellular content of guanidine is increased out of proportion to the serum content, due probably to the binding effect of the tissues.

Acceptance of the fact that there is a specific association of subacute and acute placental infarcts, lesions "D" and "E," with pre-eclampsia and eclampsia at once raises the question as to whether the villous veins or arteries are blocked and what causes the obstruction.

It would not seem rational to consider the possibility mentioned by Young<sup>2</sup> that obstruction of a maternal artery at the placental site causes the infarction. Maternal blood reaches the placental site by many arteries, the lining of which is more or less merged by the invasive action of the chorion. The maternal blood passing upward among the villi toward the fetal surface is free to circulate through all parts of the placenta. If a maternal artery should become blocked, the overlying villi are not deprived of maternal blood but are supplied by adjacent intervillous circulation.

Furthermore, infarcted areas conform to the distribution of a main villous stem and its vessels and are very sharply demarcated from the adjacent normal villi. This fact alone disproves the idea that the infarct is the result of the toxemia, for if such was the case the entire placenta should be affected and an area of necrotic villi could not be sharply circumscribed by surrounding healthy villi.

The fact that there is a dual blood supply to the villi, a fetal intravillous, and a maternal intervillous circulation, raises the question as to which plays the more important role in the vitality of the villi.

If one examines a section of placenta from a case of intrauterine fetal death late in pregnancy, the fetus having been dead a week or more, the villi are seen to preserve their form and stain somewhat deeper as though slow hyaline change was taking place and the nuclei are still intact. The villous arteries and veins show no dilatation congestion or rupture, and there is still evidence of intervillous circulation.

In marked contrast to this is the appearance of acute placental infarction. Referring to Hill and Trimble<sup>8</sup>, Figs. 7 and 13 the villi preserve their form but show marked engorgement, distention, and occasional rupture of the vessels, with enlargement and early necrosis of the villi. Thrombosis is seen in some of the villous vessels. The intervillous circulation is intact, although restricted somewhat by the enlargement and crowding of the villi. At a somewhat later stage—subacute "D" infarct—necrosis has advanced to the point of disintegration and breaking up of the villi, and intervillous circulation has not yet disappeared.<sup>7</sup> FIG. 11

In the former case—intrauterine fetal death—failure of circulation in the villi is on the arterial side through cessation of fetal heart action. The result of this is necrosis and maceration of the fetal tissues within even a few days. The placenta, however, does not macerate as do the fetal tissues. The villi preserve their form and staining reaction for several weeks or more due to persistence of the intervillous circulation, one of the two components of the dual blood supply.

It may be reasoned, therefore, that acute fulminating toxemia does not occur in intrauterine fetal death, since the intervillous circulation is sufficient to

From the knowledge gained through examination of formalin-fixed placentas from both normal and toxic cases during the past fifteen years, correlating the clinical course with the types of infarcts found in placentas (1) it appears that the "C" infarct in this case accounted for the mild evidence of toxemia between November 9 and 22. The subsequent extensive "E" infarction accounted for the fulminating pre-eclamptic condition with rapid increase in albuminuria. Had labor not been induced, it is almost certain the patient would have developed eclampsia or separation of the placenta.

### Discussion

Based on previous experience in the correlation of toxemia and placental infarction,<sup>1</sup> this case represents not a chance coincidence of acute infarction and severe toxemia but strong evidence of the probable etiologic role of thrombosis in one or more placental veins, resulting in acute infarction and acute severe toxemia.

There does not seem to be any theoretical or proved hormone, which, through inherent toxicity, could explain such a rapid increase in albumin within a period of several days. It could, however, be explained by autolysis of acutely infarcted placental tissue which produces known toxic products.

It is our firm belief that the demonstration of a specific placental pathology represents such a starting point. In 1938<sup>1</sup> we classified areas of infarction in placentas, both from normal and toxic cases. The areas of infarction, first described by Young in 1914,<sup>2</sup> were found to be specific. Knowing the clinical course of the pregnancy, one could successfully predict the type of infarct that would be found in the placenta. Conversely, on examining a series of unknown placentas, one could successfully diagnose those which had been associated with normal pregnancy and those which had been associated with toxemia.

The Lancet<sup>3</sup> in commenting on the diagnosis of toxemia of pregnancy by examination of the unknown placenta, stated, "There is perhaps nothing striking in his idea that the toxemia may be due to the absorption of breakdown products from placental infarcts, but his claim to be able to reconstruct a case of which he has no previous knowledge, would, if sustained, amount to definite proof of relationship."

The consistent association of acute and subacute infarction of the placenta with toxemia of pregnancy and the absence of these lesions in placentas from normal pregnancies have been confirmed by Patterson, Hunt, and Nicodemus<sup>4</sup> and more recently by Falkiner.<sup>5, 6</sup>

These investigators have included photographic evidence in their publications, clearly indicating recognition of, and familiarity with, the acute and subacute lesions which heretofore have been overlooked. More recently Hill and Trimble<sup>7</sup> failed to confirm these findings.

The importance of verifying the association of a specific placental pathology with toxemia of pregnancy lies in the fact that it furnishes a rational understandable basis for the toxemia and convulsions.

Placental tissue is unique in that it, alone, has the property of being eclamptogenic. While the autolysates from other tissues such as kidney, muscle, liver, etc., have been known to produce toxic effects, placental tissue is apparently the only tissue capable of yielding an autolysate which is not only toxic, but which produces convulsive seizures.<sup>8</sup> These findings were obtained by Kracke in testing the leucocytic response to injections of autolysates of various tissues into laboratory animals.

Chemical analysis of placental tissue shows that it differs from all other tissues in that it possesses a high content of arginine.<sup>9</sup> Furthermore, it possesses an enzyme, arginase, by which arginine could conceivably be broken

Referring to Spanner's diagrammatic illustration of the circulation in the placenta as shown in Fig. 32, page 26, of DeLee-Greenhill's *Obstetrics*, Eighth Edition, herewith reproduced\* (Fig. 5), it is seen that the collecting veins possess sphincters which probably serve to maintain blood in the villi and prevent overloading of the fetal heart during uterine contractions. One may frequently see sphincter-like constrictions affecting the veins on the fetal surface of the placenta causing sharply localized narrowing or almost obliteration of the lumen.

The mechanism by which these sphincters function is not clear. If, however, they should be susceptible to a hormone or internal secretion in the fetal blood previously absorbed from the mother's blood, and which is capable of causing contraction of these sphincters, constricting or even obliterating the lumen of the fetal vein, it is conceivable that such a hormone, present in abnormal amount, or insufficiently held in abeyance, might produce tonic constriction of one or more veins. The effect would be to cause marked distention of the terminal villous veins and arteries, stagnation of the circulation in the dependent villi, followed by rupture and necrosis—a picture identical with that seen in acute toxemia.

If the above sequence of events explains the formation of acute and subacute placental infarcts, why should visible thrombosis of placental veins be of such rare occurrence? Only three cases have been observed by the author in the course of many hundreds of placental examinations and these, significantly, were found in association with toxemia.

One would expect thrombosis to be the rule, on the villous side of the venous sphincters, where congestion, stagnation and necrosis occur, and it is frequently seen in microscopic examinations of infarcts. The thrombosis apparently, rarely extends beyond the sphincters toward the cord, and emphasizes the probability that it is usually hidden beneath the surface of the placenta, where it is frequently seen in the larger villous stems.

It is probable that the sphincters of certain veins react more than others, which permits the fetus to maintain sufficient circulation. Such variation is likewise seen in spasms affecting the retinal arteries. This corresponds to the finding of isolated areas of infarction in the placental substance. In some cases, however, most of the veins are involved, causing massive infarction,<sup>1</sup> Fig. 14 death of the fetus, and overwhelming toxemia. We have repeatedly observed a direct relation between the amount of infarcted tissue and the severity of the toxemia.

No statement can be made at this time as to the hormone or internal secretion which may be responsible for the probable constriction of the placental veins. However, the pathologic findings strongly indicate that venous obstruction occurs. Theorizing has been limited to that which is supported by pathologic findings. Variations in the rapidity and severity of the toxemia may be directly related to the rapidity and degree of obstruction and the number of placental veins involved.

### Conclusions

The presence of sphincters in the collecting veins of the placenta and the possibility of spasm involving the sphincters in one or more veins may well be the beginning of a chain of events leading to toxemia of pregnancy.

The case herewith reported and the associated pathologic findings strongly suggest the following sequence of events leading to toxemia of pregnancy:

1. Overstimulation of the muscular sphincters of the collecting placental veins, through overaction of, or failure to hold in abeyance an unidentified hormone or internal secretion.

\*By permission of Dr. J. P. Greenhill.

prevent acute necrosis and disintegration of the villi, even though the arterial circulation has ceased. Blockage of the venous return from the villi, however, is followed by rapid necrosis, even though the intervillous circulation is still present.

In our earlier investigations, seeking an explanation for blockage of the fetal circulation in the villi and, whether on the arterial or venous side, it was first reasoned to be due to the trauma of fetal movements on the unprotected vessels on the surface of the placenta.<sup>8</sup> However, no evidence of recent hemorrhage concurrent with the development of toxemia could be seen, and collections of old fibrin on the fetal surface of the placenta indicated the sites of former hemorrhages without associated toxemia.

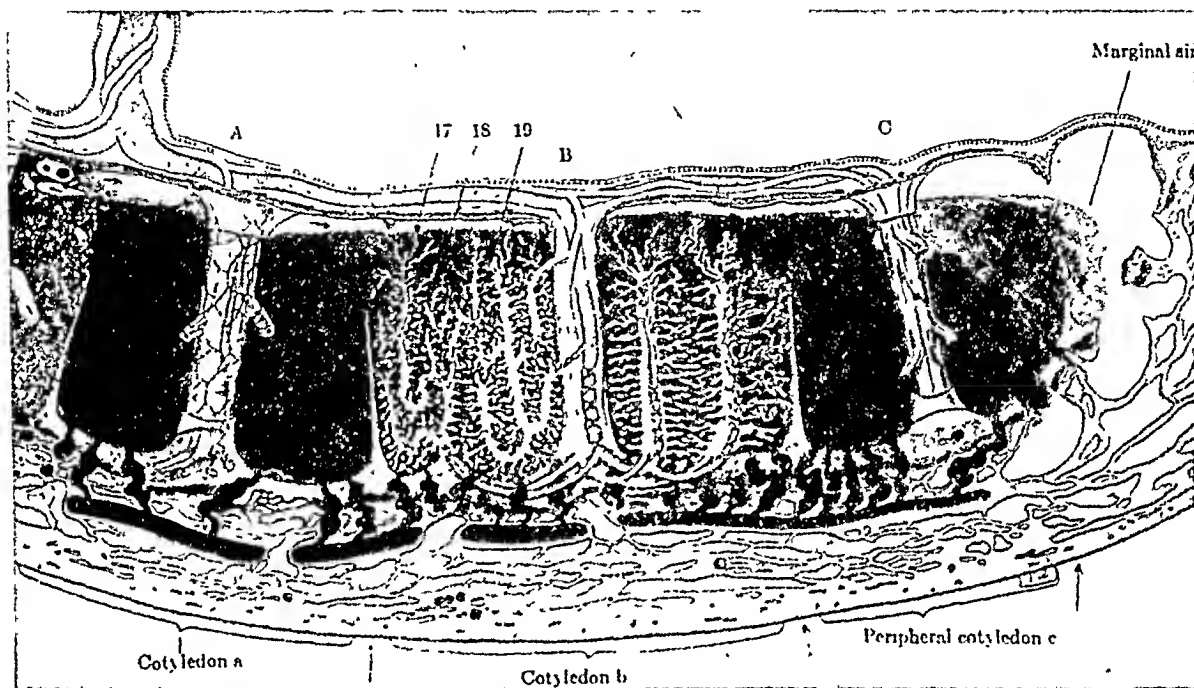


Fig. 5.—“Diagram of the Placental Circulation at Term. (From Spanner, *Zeitschrift für Anatomie*, Vol. 105, Julius Springer, Berlin, Germany.)” From DeLee, J. B., and Greenhill, J. P., *Principles and Practice of Obstetrics*, ed. 8, Philadelphia, 1943, W. B. Saunders Co., p. 26, Cotyledon “b.”

Later on it was thought that cholesterol deposits in the lining of the fetal vessels might conceivably lead to obstruction and infarction,<sup>15</sup> particularly since Patterson, Hunt, and Nicodemus<sup>4</sup> had subsequently produced such change in the rabbit's placentas with resulting infarction and convulsions. Although it was easy to demonstrate cholesterol change and deposit in the lining of the smaller villous arteries, it was not possible to find, in numerous sections examined, an area which showed proof of blockage of a villous vessel by cholesterol change and deposit. Neither was it possible to show in a convincing manner, or in a sufficiently large series of cases, that administration of iodine and thyroid lessened the incidence of toxemia through lowering the blood cholesterol.<sup>16</sup>

The distended, congested, and at times ruptured terminal villous vessels<sup>8</sup>, Figs. 7 and 13 seen in acute infarctions accompanying acute toxemia, strongly suggest *obstruction of the venous return from the villi*—an explanation recently proposed by Venable, collaborating in these investigations.

In seeking a mechanism through which obstruction in one or more fetal veins might be explained, *the presence of muscular sphincters in the veins as they leave their dependent villi may have a significant bearing on this question.*

## PODOPHYLLIN TREATMENT OF SOFT PAPILLOMAS OF THE FEMALE URETHRA

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AT THE Cook County Hospital Outpatient Gynecological Clinic we have been faced with the problem of treatment of papillomatous and condylomatous masses of the urethra and vulva. The dramatic results obtained in the treatment of the condylomata acuminata, commonly known as venereal warts, with podophyllin by Kaplan,<sup>1</sup> Tomskey and co-workers,<sup>2</sup> Culp and his associates,<sup>3</sup> and MacGregor<sup>4</sup> prompted us to apply its use in the treatment of condylomata acuminata in the female, with special reference to eight cases of condylomatous masses of the urethra—better known as urethral papillomas (Fig. 1).

The term papilloma, or soft papilloma, has often and preferably been used<sup>5,7</sup> when condyloma acuminata (venereal warts) are found in locales other than the vulva, vagina, cervix, thighs, buttocks, penis, and scrotum, namely, the urethra, anus, and face. Certainly, the gross appearance of such growths about the urethra are better described as papillomatous rather than warty, for they appear as soft, smooth, cauliflower-like moist masses arising insidiously from the external urethral meatus. Perhaps the term venereal should never be used, for it has been shown (Novak,<sup>6</sup> Taussig<sup>7</sup>) that gonorrheal infection has no scientific correlation to the condylomata. Rather, we should believe that local and chronic irritation and untreated vaginal discharges, cervical or from long-standing recurrent pelvic inflammatory diseases, are the cogent etiologic factors. It may be noted that the most common site for these condylomata in the female is the posterior half of the vulva, again giving credence to irritations from vaginal discharges or uncleanness as etiologic factors.

Condylomata acuminata are usually small, discrete, pointed, soft, pinkish-red excreescences tending toward confluence and clusters and varying from 1 mm. to the size of an orange or larger. It is interesting to note that during pregnancy they undergo hypertrophy, and may even act as an obstruction to delivery per vaginam.<sup>3</sup> The gross mass effect on the external genitals may, therefore, lead to erroneous diagnosis. In differentiation Bartholin cysts and abscesses, Wolffian duct cysts, carcinoma of the vulva, fibroma and lipoma of the vulva, and condylomata lata must be considered. Recently, a case presented itself in which there was a large firm ulcerated mass of the right labium in a woman 61 years of age, which had all the gross appearance of a carcinoma. But only after repeated biopsies a diagnosis of a condylomatous mass was made. Response to podophyllin was dramatic. Conversely, we must note that malignant degeneration, though rare, may occur.<sup>6</sup>

The microscopic picture shows a thickened but normal epithelial layer with treelike pattern hypertrophy of the papillary layer (Fig. 3). Chronic inflammation of the stroma containing lymphocytes and plasma cells is practically always present.

Treatment of the condylomata acuminata has been rather tedious and unsuccessful prior to the introduction of so simple a medication as podophyllin. Various forms of therapy including excision, cautery, fulguration, x-ray, ultra-



2. Obstruction of the venous return from the dependent placental villi.
3. Distention, engorgement, and rupture of villous capillaries.
4. Stagnation of villous circulation, thrombosis, necrosis, and disintegration of the affected villi.
5. Autolysis of the necrotic villi with dissemination of poisonous protein split-products into the maternal circulation, probably peptone histamine and guanidine.
6. Widespread damage to maternal tissues, particularly to the liver and kidneys, toxemia of pregnancy.
7. Eclamptic convulsions, due probably to hyperguanidinemia, or hemorrhagic manifestations as abruptio or ablatio placenta according to the degree of liver damage and the effect on the mechanism of coagulation of the blood.

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sions usually shrivel and drop off. In some cases no pain or discomfort whatsoever is experienced (Culp,<sup>3</sup> etc.). However, one of our cases developed a severe local reaction with marked pain. This patient had multiple neighboring condylomata which were also treated. She failed to follow instructions—neglecting to wash off the podophyllin until twenty-four hours after application.

It is assumed that the action of the drug is by local irritation, causing vascular spasm with resulting ischemia, necrosis, and sloughing.

We have seen eight cases of papilloma of the urethra, seven of which occurred without condylomata acuminata elsewhere. The ages, in the seven varied from 17 to 24 years. The other patient was 41 years of age and had the associated multiple condylomata. The urethral masses varied from 6 mm. to 52 mm. in diameter and were raised from 3 to 14 mm. Biopsies read, "epithelial papilloma (infected) with perikeratosis of the surface epithelial cells, and associated inflammatory changes of the submucosa." (Figs. 2 and 3.) Treatment with 20 to 25 per cent podophyllin was executed in the manner described. Complete disappearance resulted in the above cases. Two patients required three treatments, respectively, at weekly intervals, the other six necessitated only one treatment.

### Case Histories

CASE 1.—This patient, A. M. J., was a 22-year-old Negro woman, married, gravida ii, para ii, and complained of pain and growth in the upper portion of the vulva for four months. She first noted a small swelling the size of a pea in the region of the urethra, and experienced some burning on urination. This mass became progressively larger so that it interfered with sexual intercourse and walking. Various forms of treatment including application of salves gave no result. Past history was irrelevant. Venereal history was negative.

Examination disclosed a large, moderately firm, smooth, pinkish cauliflower mass 4 by 3 by 3 cm., protruding and covering the site of the urethra and attached by a very broad base. It was not ulcerated or tender. The cervix was clean. There were no other growths on the vulva or in the vagina. The uterus and adnexa were negative. Vaginal and cervical secretions were negative for yeast, trichomonas, and gonococcus. The urine was negative. Serology tests for syphilis were negative. Punch biopsy of the mass in two different areas revealed, "infected epithelial papilloma associated with inflammatory changes of the submucosa." This being the picture of a soft papilloma or condylomatous (acuminata) mass, 25 per cent podophyllin in a hydrosorb base was applied. The patient remained on the table for twenty minutes, then was allowed to go home, and was instructed to wash the site in six hours, using soap and water. In two days the mass was greyish-pink and had shrunk to about one-half its original size. One week after the application of medication the mass almost completely disappeared. The adjacent tissues and urethral mucous membrane were not affected. Two similar treatments were given seven days apart. No pain or discomfort was experienced, and the treatment resulted in complete disappearance of the papilloma.

CASE 2.—A. P., 17-year-old Negro girl, nulliparous, complained of "growth in my vagina, getting bigger for the past five months." Venereal disease was denied. Examination showed a mass, 7 by 35 mm., covering the urethral meatus and was lobulated, soft, moist, and pinkish red. The uterus was retroverted and the cervix everted and eroded. Trichomonads were present on hanging drop examination. The Wassermann was negative. Biopsy revealed "epithelial papilloma with perikeratosis of the surface epithelial cells." Podophyllin ointment (25 per cent) was applied with an orange stick, especially at its base, which in this case was broad. The patient remained in lithotomy for thirty minutes. No complaints were elicited. She was then instructed to enter a watertub and



violet, etc., have been tried (Kaplan<sup>4</sup>). Local or even general anesthesia was necessary in many of the procedures. Often the multiplicity of lesions made such treatment trying to both patient and physician.

The herb, Mandrake or May apple, yields the active principle, podophyllin,<sup>8</sup> a resin with marked delayed, irritant, local action. It is a pale brown to light yellow powder, turning dark when subjected to light. Twenty to 25 per cent in mineral oil, olive oil, petroleum, or lanolin have been used in treatment of condylomata acuminata.

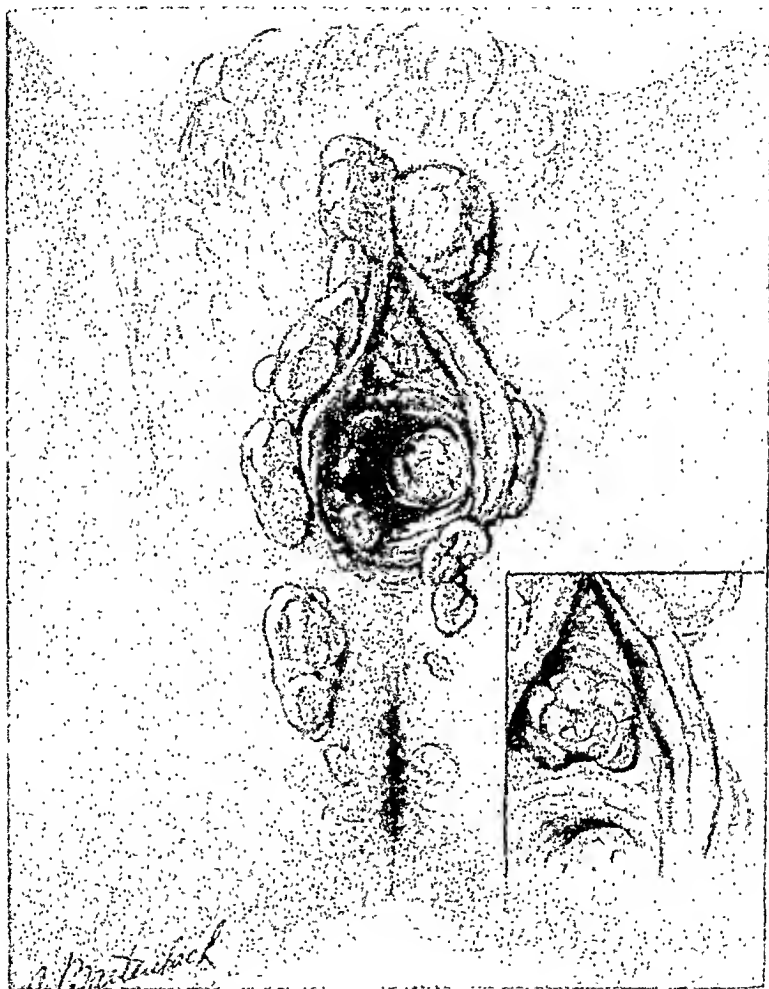


Fig. 1.—E. W., 41 years, Case No. 464013, seen in our clinic. (a) Shows papilloma of the urethra accompanied by condylomatous masses of the vulva, vagina, perineum, and anal areas. (b) Insert shows gross appearance of papillomatous mass of the urethra.

The method of treatment consisted of applying the podophyllin ointment (25 per cent) in a hydrosorb base with an orange stick to the surface, sides, cracks, and crevices of the lesions. The adjacent normal skin may be protected by either Lassar's paste, collodion, or a mild anesthetic ointment. Often the podophyllin ointment is smeared and spread, reducing its affect when the patient gets up and walks. Thus, to assure proper contact, the patient remains in lithotomy position for twenty to thirty minutes. No immediate reaction is evident, although some pain may result within six to eight hours. The patient is instructed to wash off the medication after three to six hours, using bland soap and water, preferably by getting into the tub. Mild anesthetic ointment may then be applied over the lesions. During the next twelve hours marked local inflammatory and edematous reaction occurs. On the second to fifth day the le-

wash off the medication, using a bland soap. She returned in one week. The lesion had completely disappeared. Moderate pain was experienced on the second and third days when the mass began to blanch and shrivel.

CASE 3.—R. H., 19-year-old Negro girl, complained of burning on urination and itching in the region of the urethra. Examination disclosed a soft pink mass, 10 by 3 mm., arising from the lower border of the external urethral meatus and attached by a flat short pedicle. The mass was tender when moved, and its lower anterior surface was red and ulcerated. The urine showed three pus cells per high power field. Darkfield and Wassermann tests were negative. Cervix and vagina were negative, and there was a mild degree of left adnexitis. Biopsy showed "epithelial papilloma and polyp showing ulceration, associated with inflammatory changes." Twenty-five per cent podophyllin in a hydrosorb base was applied covering the growth including the pedicle. The patient remained on the table for twenty minutes, preventing the ointment from sliding and spreading, thus diluting its effect. The adjacent tissue was protected by one of the commonly used mild anesthetic ointments. She was then dismissed and instructed to wash off the drug with ordinary soap and water. On the third day, the lesion had shriveled to about one-fourth its original size, and four days later had completely disappeared, leaving a slightly tender pink-red surface. No further treatment was given and in one week the site of the lesion was healed.

### Comment

The pathologic pictures of papilloma of the female urethra and condylomata acuminata may be considered one and the same. Treatment with 25 per cent podophyllin ointment which had been proved so highly efficacious in the therapy of condylomata acuminata was, therefore, also instituted for independent papillomas of the female urethra.

### Summary

1. Eight cases of papilloma of the female urethra were studied.
2. A suggestion of treatment with podophyllin is presented.
3. Literature to date is reviewed.
4. Microphotographic and gross illustrations of papilloma of the urethra are presented.

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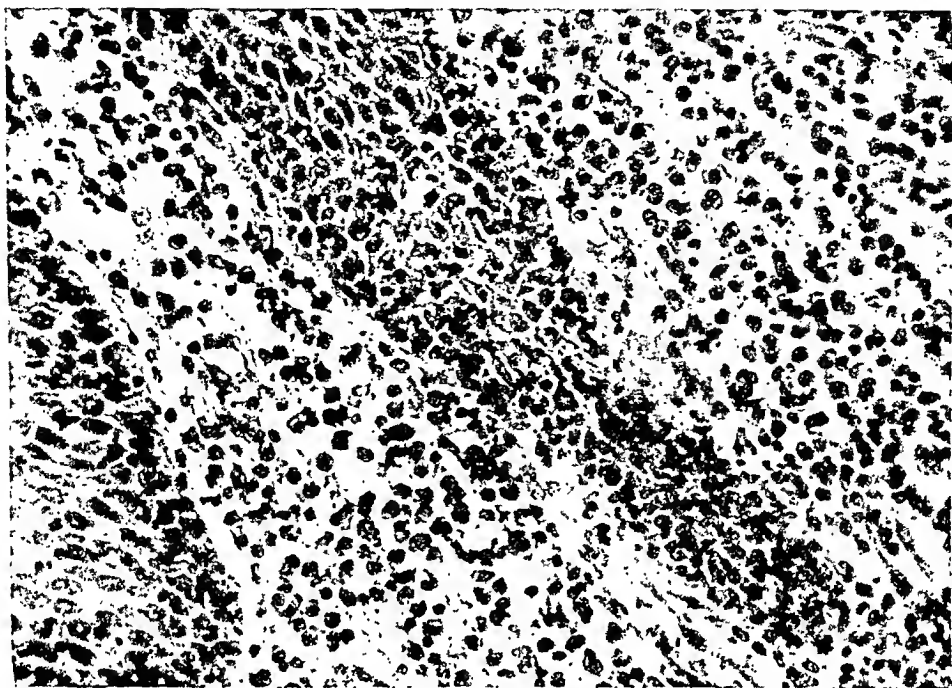


Fig. 2.—Microphotograph showing histopathologic picture of the urethral papilloma.

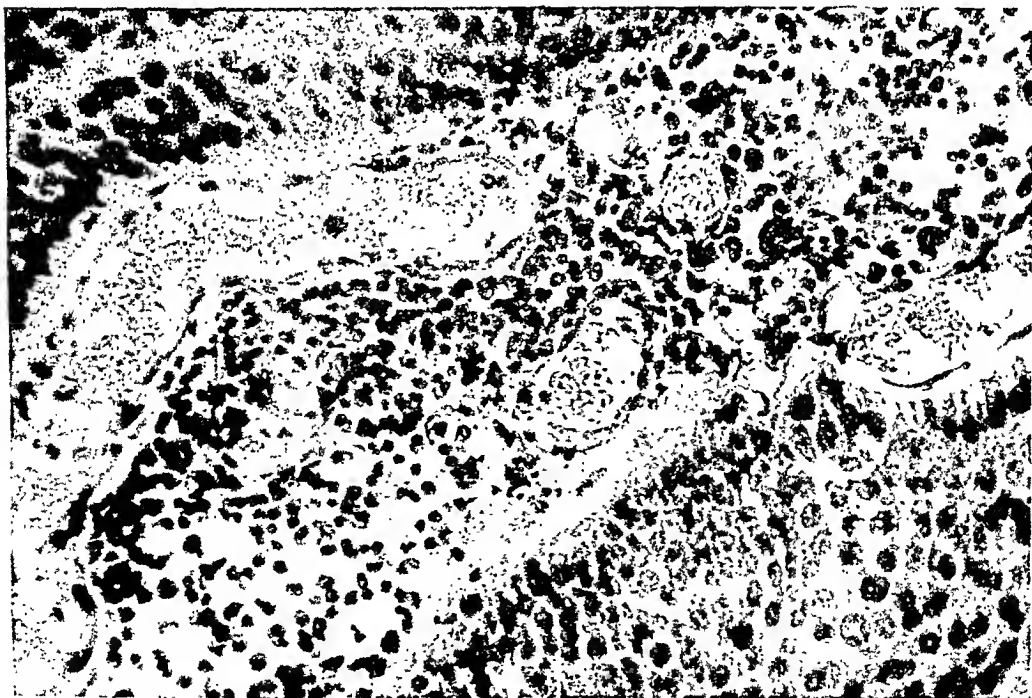


Fig. 3.—Microphotograph showing histopathologic picture of the urethral papilloma.

There is a difference of opinion among various authors as to whether these separated "islands" of endometrium undergo cyclic changes correlating with the proliferative and secretory phases of menstruation, but all are agreed that the myometrium undergoes hyperplasia and that the glands may become cystic and contain old blood resembling menstrual flow. In our experience the misplaced endometrium usually resembles the basal glands but some undoubted instances of secretory activity like that in the endometrium proper of the same uterus have been observed. Novak<sup>4</sup> states, "Not only the cyclical changes of menstruation but also the decidual changes of pregnancy may be seen in the invading endometrium of adenomyosis. In such cases the glands first become highly convoluted and secretory, and later flattened and perhaps more slit-like. The stroma cells assume the large size and the mosaic arrangement so characteristic of decidual cells."

Theories as to the cause of adenomyosis are many and need not be repeated since Brines and Blain<sup>1</sup> in 1943 stated these adequately in addition to proposing another. Novak<sup>4</sup> states, "The fact that adenomyosis represents merely an increased growth activity of otherwise normal tissues, that it does not assume the circumscribed form so characteristic of genuine neoplasms, and that the immediate normal cause of endometrial and muscle growth is the estrogenic hormone of the ovary, lends much support to the belief that adenomyosis will be found to be due to an endocrine dysfunction of the ovary."

The incidence varies according to the writer, from Dreyfuss (cited by Brines<sup>1</sup>), who reports 12.4 per cent of endometriosis and adenomyosis combined, to Levinski (also cited by Brines<sup>1</sup>), who reports 53.5 per cent, and considers it such a common finding that it may be physiologic. We feel from our observations the percentage should be about midway between these two figures if early adenomyosis is included.

It is the purpose of this paper to present additional material on adenomyosis, to clarify the term and to show that it occurs more frequently than is generally recorded. It is also our purpose to point out that this pathologic entity, adenomyosis, is capable of giving rise to definite characteristic symptoms of itself and in the absence of any associated disease in the uterus. From an analysis of our series of cases of advanced adenomyosis alone it is our belief that given a uterus with grossly apparent adenomyosis, even with associated leiomyoma, prior to the menopause, such prominent symptoms as dysmenorrhea and metrorrhagia are due primarily to the adenomyosis element rather than to leiomyoma, save for those instances where a submucous fibroid is pedunculated. In addition, we wish to reiterate Cullen's<sup>2</sup> observations that adenomyosis occurs in the earlier age groups although with less frequency than in the third, fourth and fifth decades.

All pathologic examinations and descriptions were made by one of us (W. C. H.) throughout the years covered in this paper. Definite criteria were set up for the diagnosis of adenomyosis uteri. Routine examination of the uterus included longitudinal bisection in the anteroposterior diameter. Blocks were cut to include the full thickness of the wall when possible and the diagnosis of adenomyosis was made only when endometrial islands were found to be

## UTERINE ADENOMYOSIS

### Incidence, Symptoms, and Pathology in 1,856 Hysterectomies

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B RINES and Blain<sup>1</sup> credit Rokitansky with the first description of adenomyosis. Cullen<sup>2</sup> states that von Recklinghausen was the first to give an adequate pathologic description. The first major contribution on the condition was that of Cullen<sup>2</sup> in 1908. Since then many others have amplified our knowledge of the process. For a time adenomyosis was considered a rarity, since only a few individuals recognized it as an entity. Even yet many clinicians and not a few pathologists still do not appreciate the existence, the frequency, and the importance of the condition.

Since many previous writers have adequately described the historical background, histogenesis and pathogenesis, and the many theories as to etiology, it seems unnecessary to go into these features of adenomyosis. However, we do believe that the term "adenomyosis" requires clarification and definition. Despite the fact that Fränkl<sup>3</sup> (1925) was among the first to call this entity adenomyosis, which he preferred to adenomyoma, a great deal of confusion still exists because various writers describe the process as endometriosis interna, adenomyomatosis, et cetera. It is necessary, therefore, clearly to define the term before our material is presented.

To us, adenomyosis of the uterus means heterotopic endometrium found within the myometrium, derived from the endometrium, but often losing such a connection as the process advances. It may occur locally in a small area or be diffusely distributed throughout hyperplastic musculature of one or both walls. Cullen<sup>2</sup> thus defined the condition in 1908. Adenomyosis may involve the muscle wall to within a few millimeters of the serosa but does not reach the serosa. Novak<sup>4</sup> defines the condition as a "benign invasion of the endometrium into the uterine musculature, associated with a diffuse overgrowth of the latter. In some cases the islands of mucosa may be found throughout the thickness of the uterine wall extending to the serosa itself."

It is just as possible for ectopic endometriosis to involve the surface of the uterus as for it to affect other pelvic structures, the appendix, bowel, peritoneum, et cetera. Ectopic endometriosis of the uterus always involves the outer myometrium, but never goes deeply enough to connect with the endometrium proper, and usually involves only the immediate underlying musculature. Wherever and whenever endometrium occurs in the vicinity of smooth muscle, there is hyperplasia of the latter. The present study is wholly concerned with the changes that follow heterotopia of normal uterine endometrium into the uterine musculature.

seen nearly every case had either some menstrual irregularity or dysmenorrhea. We believe this is conclusive evidence that adenomyosis alone may give rise to the characteristic symptomatology found in this condition.

Bimanual examination many times gave a clue preoperatively in these cases. Usually a globoid, slightly enlarged, and tender uterus was found. When there were leiomyomas associated with adenomyosis the uterus was more tender than when leiomyoma alone was present. In our series of 110 cases of adenomyosis alone, tenderness on bimanual examination was present 60 times. When there was only local involvement and where there was additional or more obvious pathologic changes, the diagnosis was usually not made clinically, nor should it be. The blood pressure and nutritional status gave no positive information, except that many were definitely more obese than the average. The common symptoms and findings on physical examination enumerated above are the same as those presented by Cullen<sup>1</sup> in 1908, and in a paper by Hunter and Adams<sup>6</sup> in 1931.

TABLE I. INCIDENCE OF ADENOMYOSIS IN 1,856 HYSTERECTOMIES

	NUMBER	PER CENT
Total hysterectomies	1,856	
Adenomyosis associated with other uterine lesions	517	27.8
Diffuse adenomyosis associated with other uterine lesions	139	26.8
Focal adenomyosis	243	47.0
Early adenomyosis	104	20.0
Adenomyosis in one wall only	29	5.6
Stromal endometriosis	2	0.38

TABLE II. ASSOCIATION OF ADENOMYOSIS WITH OTHER UTERINE CONDITIONS

	NUMBER	PER CENT
Adenomyosis associated with leiomyoma	304	58.8
Adenomyosis associated with uterine carcinoma	11	2.1
Adenomyosis associated with procidentia	43	28
Total hysterectomies for procidentia	153	8.2
Adenomyosis associated with ectopic endometriosis	19	3.6

TABLE III. DEGREES OF ADENOMYOSIS ALONE ENCOUNTERED IN AUTHOR'S STUDY

	NUMBER	PER CENT
Adenomyosis alone	174	33.6
Advanced focal adenomyosis	55	
Advanced diffuse adenomyosis	65	
Focal and diffuse, advanced, diagnosed grossly by pathologist	110	
Marked extensive diffuse adenomyosis	16	
Marked extensive focal adenomyosis	8	
Early diffuse adenomyosis	38	
Early focal adenomyosis	3	
Early unclassified adenomyosis	10	

Cullen<sup>2</sup> states that the uterine mucosa is often of normal thickness, while Fränkl<sup>3</sup> found hyperplastic endometrium in 11 of 30 cases. In this series the endometrial thickness was measured in each case and was found to vary from "very thin" (less than 1 mm.) to as much as 10 mm. We were unable to correlate endometrial hyperplasia with adenomyosis, even though in many cases a diagnostic dilatation and curettage was performed previously because of exces-

separated from the lining endometrium by a distance of at least two microscopic low power fields and accompanied by muscle hyperplasia. As a matter of fact, the diagnosis with a few exceptions of advanced adenomyosis was made grossly (91.6 per cent) and later confirmed microscopically. Gross findings which prompted the tentative diagnosis of adenomyosis included coarse, whorled yellowish muscle, punctate pitted areas lying within the myometrium, or dark cystic areas which extended to within a few millimeters of the serosa and eversion of the cut surfaces with rolling of the edges. All of these features were not present in each case, but enough evidence was seen to prompt the preliminary diagnosis. Since the endometrium normally extends well out into the cornu, a positive diagnosis of adenomyosis in that region was not made unless there was hyperplasia of the myometrium and very definite separation of the glands from the canal.

This present study includes 1,856 hysterectomies for all causes performed over a fifteen-year period from 1931 to 1945, inclusive, at a private hospital.\* Although the condition was called adenomyoma in the earlier years covered by this report, it is the same entity which was later termed adenomyosis and was found in 517 cases, an incidence of 27.8 per cent. We shall attempt to analyze these cases as to symptomatology, age incidence, clinical findings, pathologic types, and diagnostic criteria.

By far the greatest incidence of adenomyosis of the uterus was found in the fourth decade (259) with a lesser number in the third (120) and fifth decades (100), respectively. The youngest women were 27 years old, of which there were two. The oldest patient was 73 years of age, in whom adenomyosis occurred in conjunction with carcinoma. Cullen<sup>2</sup> reported a case in a 19-year-old girl in 1908. Since it is the general impression that adenomyosis is a disease of the climacteric or preclimacteric periods, it is emphasized that thirty-eight of our cases were under the age of 35 years, and nine were between 27 and 30 years old. In this latter group the essential pathology and basis for operation was adenomyosis, which was diagnosed clinically in six of the nine cases.

Sterility as a possible result of adenomyosis is difficult to evaluate, since the cause is found in both male and female. Sterility in adenomyosis is relatively common, but in adenomyosis there seems to be no such correlation. In this series multiple pregnancies were frequent and nulliparas were few, thus corresponding with the experience of others.

Since adenomyosis occurs so often in association with leiomyoma of the uterus, it is extremely difficult to evaluate the symptomatology. Because of this, we have chosen 110 cases of advanced adenomyosis without associated pathology for ascertaining the complaints.

In this selected group menorrhagia was the most common symptom, occurring 85 times. The other complaints in order of frequency were: dysmenorrhea, 61 times, metrorrhagia, 42 times; pain before periods, 23 times; dysuria and frequency, 9 times; pain radiating down legs, 7 times; bearing down feeling in pelvis, 6 times; and nausea and vomiting, 5 times. From this series it can be

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sive bleeding. Hyperplasia of the endometrium was not a concomitant finding; on the contrary, the endometrium was found to be normal in many instances.

If we may assume that they are speaking of adenomyosis, our findings do not agree with Schwarz and McNally<sup>7</sup> in an early article on this subject wherein it is stated that "diffuse adenomyoma rarely occurs by itself but usually coincidentally with one or more other uterine lesions." In our experience it was the only finding in 174 cases, while in other cases where coincidental pathology occurred it was the predominant factor and the basis for operation. We feel also that the characteristic symptomatology of adenomyosis often may be elicited even when it coexists with leiomyoma. The recognition of adenomyosis as a clinical and pathologic entity will result in its preoperative diagnosis in a much greater percentage of cases than in the past.

### Summary

We concur with others that adenomyosis is a distinct pathologic entity, not physiologic or neoplastic, characterized by heterotopic endometrium in hyperplastic myometrium. This may or may not be connected with the endometrium proper at the time the operative specimen is studied.

By the use of definite criteria for the clinical diagnosis and accurate gross and microscopic observations, it was found oftener and in younger age groups than has previously been reported except by Cullen.<sup>2</sup> Although by far the greatest number occur in the fourth decade, nine cases were found in women between the ages of 27 to 30 years. In each of these, adenomyosis was the chief factor, if not the only one, which caused enough distress to warrant operation. Seven of these nine cases presented adenomyosis alone. In the remaining two, one had a prolapse and the other uterus contained a small leiomyoma. Six of these were diagnosed preoperatively. Distribution with regard to age for the entire group was:

27 to 30 years	9
31 to 40 years	120
41 to 50 years	259
51 to 60 years	100
61 to 73 years	13

In arriving at our conclusions regarding the characteristic symptomatology of adenomyosis, we selected 110 cases which were adenomyosis alone by gross examination. The symptoms in this series in order of frequency of occurrence were menorrhagia, metrorrhagia, dysmenorrhea, pain before or during the menstrual period, dysuria and frequency, and a bearing down feeling in the pelvis. These symptoms when combined with the physical findings of a globoid, slightly enlarged, smooth, and tender uterus often establish the diagnosis, clinically. If the above symptomatology occurs in conjunction with a tender nodular uterus by bimanual examination, a diagnosis of adenomyosis associated with leiomyoma will usually be correct.

Adenomyosis occurs independently or associated with other uterine pathology and presents a definite symptomatology which can and should be recognized and diagnosed preoperatively.

weighing between 6 to 8 pounds. In the entire series, only one baby was born weighing well beyond that of the normal limits desired. This baby weighed slightly over 11 pounds and was delivered by cesarean section. The father and mother were both very large, each weighing over 200 pounds. Too, the pregnancy had continued well beyond the estimated date of confinement.

### Analgesia and Anesthesia

A few months after becoming affiliated with the maternity service, I was able to obtain the relatively new drug, demerol, a hydrocarbon derivative. This drug has most of the good properties of morphine but is lacking in narcosis produced by morphine on the infant, and is habit forming, but possibly less than opium derivatives. This drug, along with hyoseine, produces a very desirable state of amnesia and analgesia. Only on rare occasions did the necessity of resuscitation arise. This we found to be the most admirable characteristic of the drug. The mothers of these infants did not appear to have the prolonged narcosis after delivery so commonly seen in patients having received morphine or drugs of the same family. I will omit the details as to the administration of this medication, except to say that the usual routine was to give 100 mg. of demerol and  $\frac{1}{100}$  grains of hyoseine as soon as the patient became rather uncomfortable. Doses of both drugs were used in conjunction or separately as often as seemed necessary thereafter, and even up to or within the last one to two hours of labor. We frequently used small doses on succeeding administrations of the drug. Demerol was seldom given more than two to three times during labor.

Nearly all of the patients received drip ether for anesthesia during delivery. Occasionally nitrous oxide and oxygen were used. The chief reason for this type of anesthesia was due to lack of available anesthetists.

Caudal anesthesia was not used, as this type of anesthesia was impractical for our hospital unit due to lack of trained personnel and adequate equipment to assist the attending obstetrician.

### Types of Deliveries

Less than one-third of our patients delivered spontaneously. This is quite the reverse of the figure reported by Newburger<sup>1</sup> from a similar group of civilian hospitals where 78.8 per cent were delivered by this method. This probably can be accounted for in several ways, but the most plausible reason, I believe, is that we were delivering so many women who were giving birth to their first child. It is my opinion that low forceps and episiotomy is a method of choice if one has had adequate training.

Our incidence of midforceps is rather great compared with those done in Cook County, Illinois. Our percentage was well over 3 per cent, while Newburger's figures show only 1.2 per cent. This may appear to be radical obstetrics, but I do not feel such is the case when consideration is given to the fact that no stillbirths resulted in this group. I also believe that each of these cases were duly considered, and that ample reason could be given for each case so delivered. It would require too much detail to explain each case thoroughly, indicating why the method of delivery was selected.

A number of cases which presented posterior positions of the fetal head were delivered by the forceps maneuver described by Bill.<sup>2</sup> These cases might rightfully be placed in the midforceps group, since that is actually what each case represents. Of course, this could increase the incidence of midforceps. These are not included, as they might well be placed in the low forceps group by those who do manual rotations and allow their patients to go further and

# A GENERAL SURVEY OF MATERNAL CARE IN A NAVY HOSPITAL

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THE purpose of this survey is to review the status of maternal care rendered by Navy physicians during and shortly after the recent military emergency on one of the many military posts in this country. Furthermore, I wish to use this report as a comparative measure to some of the results obtained in civilian hospitals where a similar number of cases were cared for. In such a way we may be able to formulate some opinion as to whether the services rendered were inferior, equal, or superior to that in civilian life.

Our present report deals with an estimated 1,500 to 2,000 prenatal cases and approximately 500 deliveries for the stated period.

In reviewing the literature, I was able to find a survey prepared by Newburger,<sup>1</sup> which gave a thorough and comprehensive study of all the obstetric activities in Cook County for the year of 1944. Newburger grouped the hospitals according to the number of deliveries per hospital, which ranged from 50 or less to 1,000 or more deliveries per year. There were five hospitals in the group which had 350 to 499 deliveries per year. It will be with this last group that our comparative results will deal. I feel that we might expect as satisfactory results from the Chicago area as any other place in the country, since this is an outstanding medical center in the United States, and by so doing there will be no unfair advantage.

## Prenatal Care

Most of our prenatal care and deliveries were done by or supervised by men with American Board qualifications or the equivalent thereto.

In our prenatal clinic we followed to a great extent the same routine as that in any well-organized clinic. The patients were usually first seen after having missed their second menstrual period, unless the occasion demanded an earlier visit. From then on to the last two months of pregnancy, the patients visited the clinic every three or four weeks. During the last two months they were seen every one or two weeks, depending on the patients' condition.

Patients were watched closely for any toxemic symptoms, treated immediately, and observed frequently when such symptoms were discovered. We had about the usual number of patients presenting the ordinary nausea and vomiting. There were very few, probably 1 per cent, which required hospital treatment for this condition, and none of these were of severe nature. Our more advanced states of toxemia were also very rare, and only one or two occasions can I recall a case in toxemic state which was of the group that required hospitalization. No cases of eclampsia per se were encountered.

Weight was watched closely. Weight gain of 20 pounds or less for the entire pregnancy were accentuated and demanded. I believe that this was one, if not the all-important factor in the large percentage of short labors observed in most primiparous women where so many three- to ten-hour hospital labors were seen in this group. Most of our babies were small, usually

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## Fetal Monstrosities and Abnormalities

We encountered abnormalities of fetus more often than is commonly noted. There were six infants born with spina bifida. All of these were full-term or very close to full-term pregnancies. Two of these had associated hydrocephalus. There was one each of the following: Mongolian idiot, congenital heart, and bilaterally clubbed feet. This gave us an instance of nearly 2 per cent. Our number of spina bifida infants was completely out of place according to the studies of Mall and Panum, where they rated fifth in the group of deformities.

Mall differentiates between abnormal and pathologic monsters, those of the first group being germinal in origin, while those of the second group acquired abnormalities having been developed from normal ova with changes due to external influences. He states that the number of monsters which develop to full term is approximately 0.6 per cent, and that three out of every four are aborted in the early months. If this is true, our incidence of monstrosity would have been roughly 8 per cent as compared with 2.6 per cent for the general population. This is a tremendous increase. How can it best be explained? Is life in the military service conducive to such defective offsprings?

There have been a number of arguments against the germinal theory and in favor of the environmental element. In favor of the latter is such evidence as that noted by Keibel and Mall, where 96 per cent of tubal pregnancies showed pathologic ova; Greenhill's idea of faulty relation between placenta and fetus giving rise to developmental arrests; and finally experimental production of spina bifida by the action of sodium salts on normal embryos.

Adair, when investigating malformations in twin pregnancies, came to no final conclusions, but did believe more in the fetal origin in view of constant association of hydramnion with monster twins, and thinks that we should find similar deformities in monozygotie twins. In this group of spina bifida, we had twin boys with a similar spinal defect. This fully satisfies the requirement and also presents another angle to the picture. The mother of these twins presented herself as a sterility problem about one year before. With the aid of an urologist we studied both partners. The husband had an abnormal spermatozoa count. Both partners were treated and the twin pregnancy was soon obtained. Titus states that he is entirely convinced that there is a possible development of a monstrosity when a healthy ovum is fertilized by an abnormal or deformed spermatozoon and cites a similar case to that just described. This leaves us with further thought, questioning whether military life is a contributing factor in giving rise to defective sperm and ovum and in turn a larger incidence of monstrosities.

## Maternal and Infant Mortality

We are proud of the results that fall under this heading, since we had no maternal mortality during this entire period. Newburger, reporting for a similar number of patients in Cook County, Illinois, found the maternal mortality to be 6 per 1,000 cases.

Our stillbirth rate was extremely low, with only one stillbirth from a prolapsed cord in a breech presentation, one from placenta abruptio, one of an unknown cause, and two due to hydrocephalus. In each instance of hydrocephalus destructive operations were necessary. Actually, this leaves only one or two stillbirths which might be attributed in some way to the obstetrician. Again, comparing with Cook County records, we find an incidence of 46 stillbirths per 1,000, or 22.7 per cent. Our neonatal losses were practically neg-

await the forces of labor to bring about the descent of the head. If the above procedure is used, it may mean a longer labor and possibly two anesthetics for a patient. This method cannot be criticized for those who do not feel adequately trained in the use of forceps.

Our incidence of cesarean section was very low, 1.3 per cent. I attribute this to the practice of conservative obstetrics followed in our hospital. Newburger's report gave an incidence of 3.1 per cent. Falls states that some hospitals run as high as 14 per cent. This he considers "letting the physicians run wild." Such a percentage is appalling. I realize it is easier to use section as a "way out" in private practice when the doctor is constantly harassed by the husband and in-laws. No doubt in many cases this is not a reflection on the individual's background in obstetrics and lack of sound judgment in selecting the proper method of delivery, but rather a loss of will power and fortitude. This, in so many instances, means that the patient is doomed for one or more sections in the future, following the rule that so many use, "once a section always a section."

I do not believe our deliveries by breech extraction and version with breech extraction differ significantly from those of Newburger's or any other hospital, unless the more radical procedures of "breaking up breeches," and the converting of all cephalics to breeches is practiced.

### **Toxemia, Postpartum Hemorrhage, and Infections**

As already stated, a case of toxemia was seldom encountered. When present, these were usually mild, and I do not believe we had over three or four cases that could be placed in the pre-eclampsia group. There were no cases of eclampsia. These results I think can be credited to proper prenatal care plus the aid of a group of intelligent women with whom we had to deal.

The number of postpartum hemorrhage cases was likewise small. Only three cases were listed. Newburger reports 1.3 per cent. There were possibly a few other cases that might be listed on the borderline. Some of these were packed as a method of treatment. This method was not followed unless it was believed to be the last resort. I feel this only gives the patient a greater chance of becoming infected. This is certainly true when one considers that the resistance is already lowered due to blood loss, which has brought to the front this method of treatment. There was no mortality in the group of postpartum hemorrhages.

We had a number of patients who revealed some evidence of infection post partum. Nearly every incidence of this was mild and rather easily controlled by sulfonamides and penicillin when indicated. Here again there was no mortality. Newburger reports 3.2 per cent infections. Ours did not differ significantly from these. It seems to me that death from infection in obstetrics should readily pass, if it has not already, from the position it has held throughout the years as a leader in maternal mortality to a far less prominent role. As I look back over approximately 10,000 cases with which I have been connected I can recall only a rare instance of a maternal death from infection during childbirth. I feel that this should be universally true due to the help of our modern drugs and the practice of better obstetrics. However, take the state of Illinois for example. During the year 1944, the vital statistics showed that infections led the list for maternal deaths being responsible for 24.2 per cent, toxemia 16.7 per cent, and hemorrhage 16.3 per cent. Yerushalmy, in reviewing the maternal mortality in the United States for the years 1941 and 1942, found a 10 per cent reduction in deaths due to infection, 11 per cent due to toxemia, but no reduction due to hemorrhage. This shows a definite improvement toward reducing two of our major complications.

## METASTATIC CHORIONEPITHELIOMA OF THE LUNG TREATED BY LOBECTOMY

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ALTHOUGH a chorionepithelioma is usually a highly malignant tumor, it may at times manifest an extraordinary digression from the usual clinical course. Unless hysterectomy is performed early, many cases go on to a rapid, fatal termination. Pulmonary metastases occur frequently and often grow rapidly, and are important factors in mortality. Some cases of chorionepithelioma, however, run an atypical course. Cases have been reported in which there was incomplete removal of tumor tissue at the time of hysterectomy, and yet the remaining tumor disappeared spontaneously and the patient was well even years after operation. Regression and even disappearance of pulmonary metastases, either spontaneously or following radiation therapy, have been reported. Whereas an analysis of the literature reveals an appreciable number of cases of spontaneous disappearance of residual tumor in the pelvic region, there are only a small number of cases on record in which recovery has followed the presence of definite pulmonary metastases.

Cases of so-called ectopic chorionepithelioma have been reported in which no evidence of a primary tumor was found in the pelvic organs. Therefore, in some cases the chief factor in management is control of the metastatic lesion. The case which we are herewith reporting falls into this category.

### Case Report

K. W., a 32-year-old woman, had a miscarriage in 1935 and was delivered of a normal child in 1937. In 1939 occasional vaginal bleeding occurred for about three months. Operation for the removal of an hydatidiform mole was performed in October, 1939. A second dilatation and curettage was done in November, 1939. During the following two years eleven Aschheim-Zondek tests were done and found to be negative, but no roentgenogram of the chest was made. In April, 1942, irregular menstrual bleeding began. A roentgenogram of the chest then showed a small nodule in the right lower lung field. An Aschheim-Zondek test done at the same time was reported negative. A second roentgenogram taken in September, 1942, showed that the mass in the right lung had more than doubled in size when compared with the film taken five months previously. In October, 1942, the Aschheim-Zondek test became positive. The following month another dilatation and curettage was performed, but examination of the tissue revealed no tumor or decidua tissue. The patient had amenorrhea from August, 1942, to January, 1943, and during this time the mass in the lung increased in size. In November, 1942, radiation therapy was given to the chest over the site of the tumor; 2,100 roentgens total was given to each of two fields through 10 cm. circular ports at 70 cm. target skin distance, 1,000 K.V. A daily dose of 300 roentgens was given to alternating fields. Following therapy there was little change in the size of the mass, as seen on the roentgenogram. Another Aschheim-Zondek test in November was again positive. In March, 1943, the first hemoptysis occurred and there was roentgen evidence of further enlargement of the mass in the right lung (Fig. 1). On the basis of the history of the hydatid mole with the subsequent appearance of a mass in the lung, together with positive Aschheim-Zondek tests, a diagnosis of metas-

ligible. I can recall only one or two instances compared with 35 per 1,000 in Cook County. I am considering infants in my report who had reached six and one-half to seven months of gestation. Therefore, there may be some fallacy here in comparing our statistics with that of Newburger, since he does not state the Illinois law on the age of viability for births. Using Cook County as a whole, the following mortality rates were given per 1,000 for the year 1944: stillbirths, 20.4 per cent; neonatal, 20.1 per cent; and maternal, 1.7 per cent.

It is also interesting to note that the highest stillbirth rate came from home deliveries, although only 9.7 per cent fall in this category. This is a figure for the state of Illinois as a whole, and may well be attributed to inadequate facilities as well as improper care.

### Summary

1. It would appear from this report, although it does not cover a large number of prenatal patients but over a considerable period, that Navy maternal care may compare as well, if not superior, to that of the average hospital dealing with similar number of deliveries.

2. Mortality rates were notably lower.

3. The incidence of cesarean section was very low, 1.3 per cent, compared with the usual range of 3.5 per cent to as high as 14 per cent in some hospitals. I believe this reveals conservative obstetrics, but not too conservative in view of our mortality rates in both infants and mothers.

4. The absence of eclampsia and small number of toxemia indicate adequate prenatal care.

5. The number of fetal deformities is extremely high, particularly of cranio-rachischis. Why this should be true is only a matter of conjecture.

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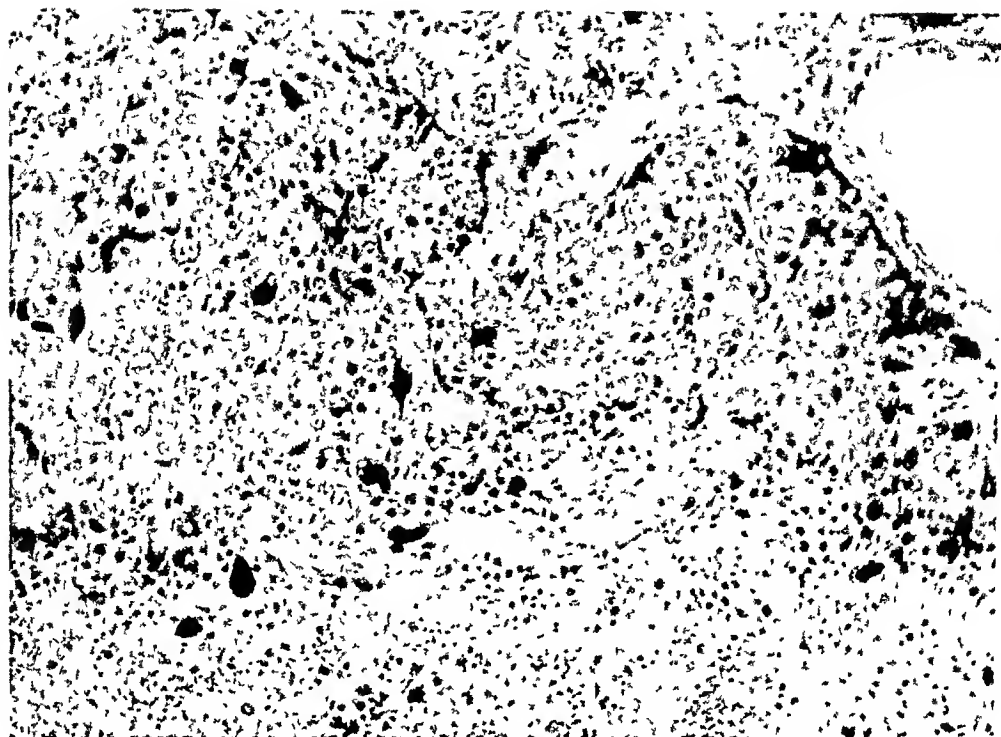


Fig. 3.—Photomicrograph of pulmonary lesion showing characteristics of chorioneplithelioma.

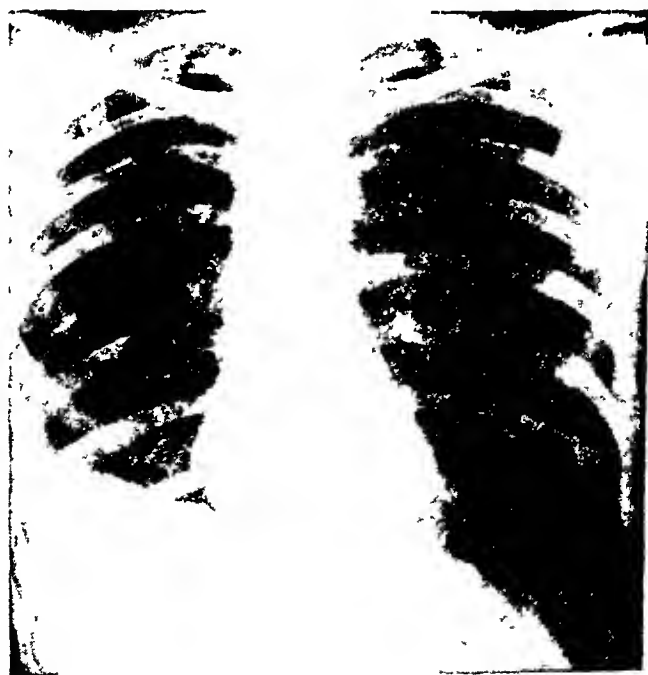


Fig. 4.—Roentgenogram of chest one and one-half years after right lower lobe lobectomy.



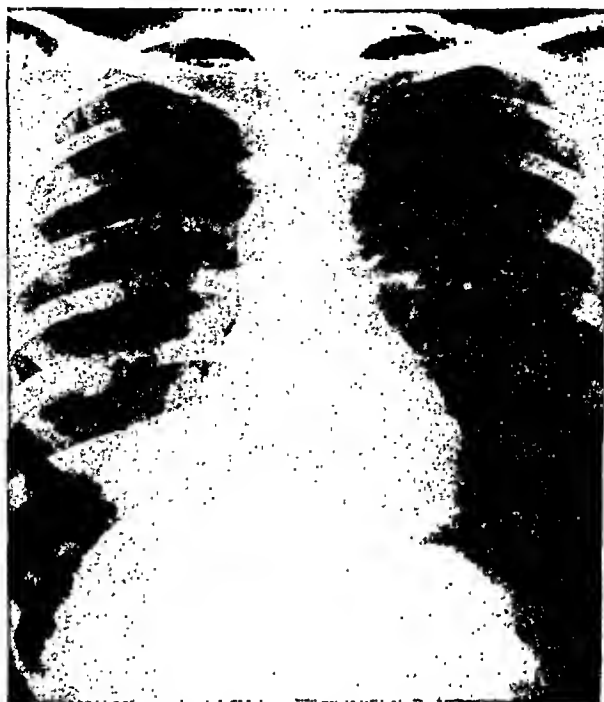


Fig. 1.—Preoperative roentgenogram of chest showing mass at base of right lung.

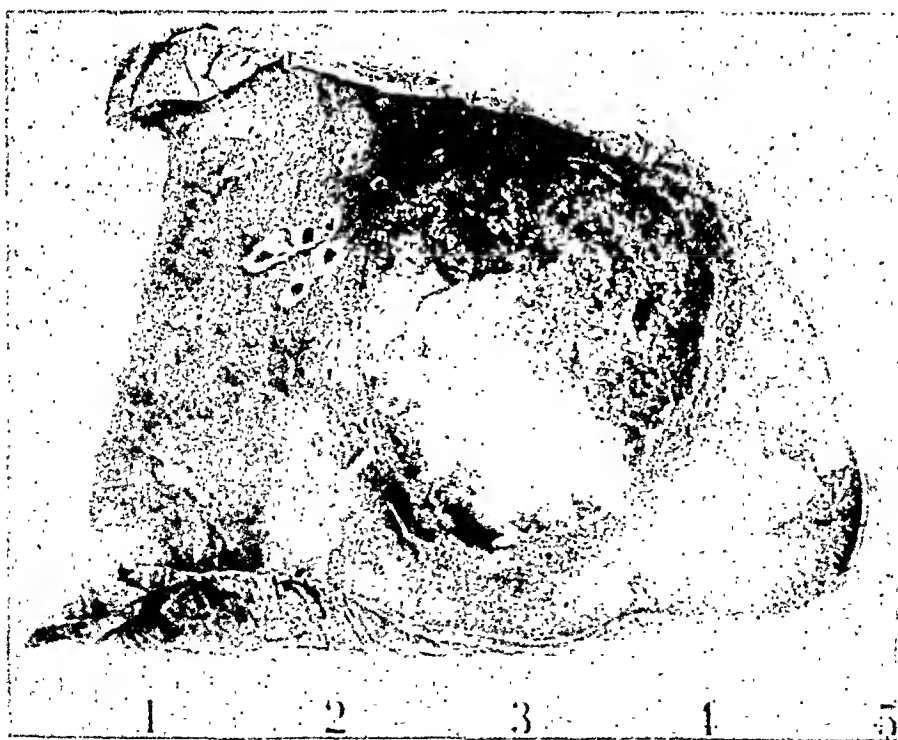


Fig. 2.—Operative specimen showing large metastatic chorionepithelioma in lung.

# PRELIMINARY CLINICAL REPORT ON A NEW SYNTHETIC ESTROGEN, MEPRANE\*

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IT IS the purpose of this article to report on the clinical effect, the therapeutic dose, the estrogenic potency, and the toxicity of the synthetic estrogen, "Meprane" (3,4-Bis, M-methyl-propionoxy-phenyl, hexane)\* in patients with the menopause syndrome.

## Material and Methods

This study was limited to those patients who complained of typical menopausal symptoms following excision of both ovaries, so that the effect of the drug would not be confused by residual ovarian function. Thirty-four consecutive patients, who had had castration operations at the Free Hospital for Women from two months to 9 years previously (Table I), were followed for one to three months after meprane therapy.

TABLE I. INTERVAL FROM CASTRATION OPERATION TO TREATMENT. 34 CASES.

0-3 MONTHS	3-6 MONTHS	6-12 MONTHS	1-2 YEARS	2-5 YEARS	5-9 YEARS
15	3	9	2	2	3

TABLE II. AGE AT START OF TREATMENT. 34 CASES.

25-29 YRS.	30-34 YRS.	35-39 YRS.	40-44 YRS.	45-49 YRS.	50-54 YRS.	55-59 YRS.
4	0	6	13	5	5	1

The age distribution of these patients is given in Table II.

The clinical symptoms of each one were tabulated at the first visit, including the patient's estimate of the number of hot flashes per hour or per day, the incidence of headaches, of drenching night sweats, of irritability, insomnia, breathlessness, and so on. A control vaginal smear was then taken. In almost all cases, an initial dose of 3 mg. daily of meprane was prescribed for four weeks. Two patients were given a small dose of phenobarbital, but no other drugs were used in this series. On the return visit, a second smear was taken and the clinical effect of the previous dose evaluated. If symptoms were almost entirely relieved, a maintenance dose of 2 mg. daily was prescribed for the second month after a ten-day interval without medication. When symptoms were only partially relieved by the initial dose, 6 mg. daily were prescribed for a shorter period of two weeks. A few patients failed completely to respond to the initial dose; these "failures" are briefly mentioned below.

The estrogenic potency of meprane was measured by comparison of the smears taken on the last day of a month's treatment with the pretreatment smears.

\*Generously supplied for this study by Reed & Carnrick, Jersey City, N. J.

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tatic chorionepithelioma of the lung seemed most probable. The possibility of an independent tumor of the lung could not be entirely ruled out because of the relatively slow growth and the failure to find evidence of tumor in the pelvic organs. Because of the atypical course of the tumor, it was felt justified to remove the pulmonary mass, even though it might be a metastatic lesion. Consequently, on March 25, 1943, a right lower lobe lobectomy by the hilar dissection technique was performed. The postoperative course was entirely uneventful. An Aschheim-Zondek test done a day before lobectomy was positive, whereas another test done a day after operation was negative. Pathologic report of the lobe of the lung was as follows:

Dissection of the lower lobe bronchus and branches showed no evidence of obstruction. On section there was a large, ovoid, circumscribed tumor mass measuring 6.5 by 6 by 5 cm. which did not involve a bronchus (Fig. 2). About three-fourths of a centimeter from this mass was a second small nodule less than one centimeter in diameter. On cut section the main tumor mass, as well as the other small nodule, was very hemorrhagic in the center, and elsewhere white and rather granular looking. There appeared to be a direct extension of the tumor into an adjacent anthracotic peribronchial lymph nodes. On microscopic examination the findings were typical of chorionepithelioma (Fig. 3).

On April 27, 1943, a complete hysterectomy and bilateral salpingo-oophorectomy were performed. At the time of operation no tumor tissue was visible in the pelvic organs. Careful examination of the entire specimen failed to reveal the presence of any tumor in the uterus or adnexa.

Over three years have elapsed since lobectomy was performed, and the patient has been in excellent general condition, free of all symptoms or evidence of disease, and repeated roentgenograms of the chest have failed to reveal any further pulmonary metastases (Fig. 4). Aschheim-Zondek tests have been done at regular intervals and all reports have been negative.

This case is an example of a chorionepithelioma running an atypical course. Whereas in most instances the pulmonary metastases grow rapidly and cause a fatal outcome in a matter of weeks, it is known that a pulmonary metastasis was present in our case for at least eleven months prior to its removal by lobectomy. Radiation therapy seemed to be of little benefit in our case, but this statement should not be interpreted as inferring that irradiation is not of value in some cases of metastatic chorionepithelioma. Realizing that we were dealing with an atypical case of chorionepithelioma, an attempt to remove the pulmonary metastasis by lobectomy seemed justified. We feel that the lobectomy was of great value in the treatment of this particular patient, but realize that a similar procedure would rarely be applicable in chorionepithelioma with pulmonary metastases. Whether the panhysterectomy done following lobectomy has been a factor in the failure of the patient to show further evidence of disease can only be conjectured.

### Summary

A case of metastatic chorionepithelioma of the lung successfully treated by lobectomy is reported. The Aschheim-Zondek test which was positive prior to operation became negative following lobectomy. Panhysterectomy performed a month after lobectomy failed to reveal any evidence of disease in the pelvic organs. The patient is well and free of evidence of disease over three years following pulmonary lobectomy. The plan of therapy pursued in this case could be feasible only in a very small percentage of cases of chorionepithelioma.

On the basis of relief of symptoms in this group of patients, the optimum maintenance dose appears to be about 3 mg. daily. Those who respond poorly to this generally will not obtain very marked relief, even when the dose is doubled.

*Estrogenic Potency.*—All pretreatment vaginal smears were graded, according to the degree of cornification, into four classes of estrogenic activity, from those that were atrophic and showed none, to those showing marked estrogen effect. There were 48 post-treatment smears to compare with the original controls. In all but one case, the given dose maintained or increased that degree of cornification seen in the control slide. Although it was not possible accurately to correlate the degree of response with the dosage level employed, there was no question that this drug effectively produced the picture of cornification of the vaginal mucosa characteristic of potent estrogenic stimulation (Table V).

TABLE V. EFFECT ON VAGINAL MUCOSA

	VAGINAL CORNIFICATION			
	NONE	MINIMUM	MODERATE	MARKED
Before treatment				
34 smears	11	9	11	3
After treatment				
48 smears	0	7	17	24

*Toxicity.*—Complaints of the usual so-called toxic effects after the doses given to this group of patients were conspicuous by their absence. Twenty-seven of the 34 patients on close questioning had no subjective complaints suggestive of toxicity. Those listed in Table VI were presented by four patients referred to above as "failures," and three others in whom such symptoms were mild.

TABLE VI. INCIDENCE OF SUBJECTIVE TOXIC COMPLAINTS AFTER MEPRANE. 34 CASES

HEADACHE, VERTIGO	TIRED FEELING	NAUSEA
5	2	1

It is probable that the four patients who were responsible for most of these complaints should not have been selected for estrogen therapy in the first place, and the significance of their complaints is therefore suspect. The complaints of the other three were negligible. There was no diarrhea or urticaria.

In 15 patients, blood and urine studies were done before and after a course of meprane to uncover any evidence of untoward effects of the drug on hematopoietic, hepatic, or renal systems. No decrease in hemoglobin per cent or in polymorphonuclear count, and no interference with platelet function as tested by bleeding and clotting times could be demonstrated. The value of nonprotein nitrogen was within normal limits after treatment, and the urine showed no signs of kidney damage. Blood creatinine levels and total protein were not significantly affected. The icteric index did not rise. Blood uric acid and blood chloride values remained normal.

These studies tend to confirm the clinical impression that the doses of meprane employed in these patients had no consistently demonstrable toxic effect.

### Summary and Conclusions

1. The synthetic estrogen, meprane, was used in 52 courses of treatment in 34 unselected patients with the menopause syndrome after castration operations.

The incidence of toxicity was deduced from the occurrence of the usual subjective symptoms—nausea, headache, vertigo, etc., and further checked by selected blood and urine studies in 15 patients done both before and after meprane therapy.

Results

*Clinical Effect.*—It is notoriously difficult to evaluate in absolute terms the degree of relief from purely subjective symptoms after any medication. However, in this group, 23 of the 34 patients obtained almost complete relief from meprane; seven others were more than 50 per cent relieved, while four failed to respond subjectively to the drug (Table III).

TABLE III. ESTIMATED RELIEF OBTAINED

NO. OF CASES	80-100% RELIEF	50-80% RELIEF	NO RELIEF
34	23	7	4

Three of the four "failures" discontinued medication after five, eight, and twenty-one days respectively, because of disagreeable headache, vertigo, or a "tired feeling." Two of these were not relieved subsequently on other estrogens, and it was felt that there was a large psychogenic component in their syndrome. The other two had shown a marked cornification of their pretreatment vaginal smears; in one this reflected previous stilbestrol therapy and in the other, it was later found that the surgeon had left behind part of one ovary. In both of these patients, the complaints may not have been wholly caused by a marked estrogen deficiency, and therefore have little significance.

*Therapeutic Dose.*—Fifty-two courses of treatment, usually of four weeks' duration each, were given the 34 patients, and the dosage was varied as stated previously in an attempt to establish the optimum therapeutic range for this syndrome. The decrease in frequency of hot flashes following meprane therapy was used as the best indicator of the effectiveness of a given dose, as suggested by Albright, Halstead, and Cloney.<sup>1</sup> In all but one case, hot flashes recurred during the ten-day interval of no medication that preceded each successive course. Table IV summarizes the relief of hot flashes obtained from the three different dose levels employed. In brief, it was found that about two-thirds of the cases given 2 mg. daily were satisfactorily relieved; disregarding the four "failures" for reasons given above, it was found that about three-fourths of those on the next higher dose level responded well, but five of the eight more refractory cases that were given double the usual dose failed to obtain more than partial relief therefrom.

TABLE IV. EFFECT OF DIFFERENT DOSES OF MEPRANE ON FREQUENCY OF HOT FLASHES

DOSE	NO. OF COURSES OF TREATMENT	ESTIMATE OF PER CENT DECREASE IN HOT FLASHES		
		80-100%	50-80%	NONE
2 mg. daily	17	11	5	0
63 mg./month				
3 mg. daily	27	17	6	4
84 mg./month				
6 mg. daily	8	3	5	0
84 mg./2 weeks				
Total	52*	31-61%	16-31%	4-8%

\*In one case, hot flashes did not recur during the interval preceding a subsequent course of therapy.

## MENINGITIS FOLLOWING CONTINUOUS CAUDAL ANESTHESIA

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THE place of continuous caudal anesthesia in obstetrics remains a controversial issue. It is, therefore, important to report complications arising after its use.

A 23-year-old gravida iii, para ii was admitted to Parkland Hospital on July 18, 1946, four hours after premature onset of labor. The estimated date of confinement was August 26, 1946, since the last menstrual period began on November 19, 1945. The two previous pregnancies also terminated prematurely, but resulted in surviving children weighing 1,360 and 1,590 Gm., respectively, at birth.

Examination after admission revealed a patient in active labor with the child presenting in left occipitoanterior position, the cervix 2 centimeters dilated and largely effaced. The maternal temperature, pulse, and respiratory rates were normal. Two hours after admission, caudal anesthesia by the catheter technique was begun. The skin was prepared with green soap, alcohol, and zephiran chloride solution. A No. 4 plastic catheter was inserted into the caudal canal through a No. 16 gauge needle, and fixed in place with waterproof adhesive tape. An initial test dose of 10 c.c. demonstrated the absence of spinal anesthesia and, therefore, the extradural position of the catheter. During the ensuing two and one-quarter hours, four instillations of 1.5 per cent metycaïne solution, totaling 75 c.c., were made. Because labor did not progress, the anesthetic was discontinued, but the catheter remained in place. The patient became restless and seemed to be more agitated than the severity of the labor pains warranted. Seven and one-quarter hours after admission and eleven and one-quarter hours after onset of labor, complete dilatation was attained, with the head on the perineal floor. An additional instillation of 25 c.c. of 1.5 per cent metycaïne solution was done to permit outlet forceps delivery of a 2,041 Gm. living child, with minimal maternal blood loss. The patient was returned to her room with normal temperature, blood pressure, pulse, and respiratory rates. The catheter remained in the caudal canal for five and three-quarter hours, and the patient received five instillations, totaling 100 c.c. of 1.5 per cent metycaïne solution. This represented a total dose of 1.5 Gm. of metycaïne.

The following day, twenty-four hours after removal of the caudal catheter, the temperature suddenly rose to 104° F. and the pulse rate to 100. There was nuchal rigidity, hyperactive reflexes, and flexure movements of ankle, knee, and hip upon passive flexion of the neck. In addition, there was moderate tenderness and hyperemia over the presacral area. The cerebrospinal fluid, obtained by lumbar puncture, was cloudy and under slightly increased pressure. The cell count was 3,000 per c.c., and all of them were polymorphonuclear leucocytes. A smear revealed gram positive cocci, but no organism grew on the usual laboratory culture media.

The treatment for meningitis consisted of 10,000 Oxford units of penicillin intrathecally, 50,000 intramuscularly, and 5 Gm. of sulfadiazine orally. Continuation therapy included 50,000 Oxford units of penicillin intramuscularly every three hours, and 2 Gm. of sulfadiazine every four hours, for the next five days. Two days after onset of the meningitis, the cerebrospinal fluid was less cloudy and contained only 350 polymorphonuclear leucocytes per cubic centimeter. Ten thousand Oxford units of penicillin were injected intrathecally at this time.

2. The drug proved to be effective in the relief of symptoms in 30 of the 34 patients; the remaining four were probably unsuitable for estrogenic therapy.

3. The optimum therapeutic dose for the menopause syndrome from this study appears to be of the order of 2 or 3 mg. daily; this causes moderate to marked cornification of the vaginal mucosa, as demonstrated by vaginal smears.

4. The estrogen, meprane, seems to be remarkably free from toxic reactions when used in doses up to 6 mg. daily for two weeks. Although a few patients complained of headaches or vertigo, gastric symptoms were essentially absent, and blood and urine studies revealed no demonstrable effect on the formation of blood constituents or on liver or kidney function.

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32 CUMBERLAND AVENUE.

## THE DANGERS OF THE INTRACERVICAL PESSARY AS A CONTRACEPTIVE DEVICE\*

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THE more recent literature devoted to gynecology universally condemns all types of intrauterine and intracervical devices designed to achieve prolonged contraception because they are both ineffective and dangerous. In addition to citing proof of their unreliability as contraceptives, many gynecologists have reported the occurrence of all varieties of ascending pelvic infection following the use of such unorthodox paraphernalia. In fact, more than a dozen deaths have been directly ascribed to complications following their insertion. For these cogent reasons, the injunction concerning such devices as contraceptives is so stringently observed by some gynecologists as to prevent them from using similar pessaries in the treatment of dysmenorrhea.

Aware of these critical sentiments, the authors were recently surprised to encounter three women suffering from pelvic inflammation resulting from the same type of intracervical contraceptive device. Inasmuch as the three patients had emigrated to South Carolina from the same section of the United States within a period of six weeks of each other, and because each of them had had a rubber-covered, valvelike, wishbone pessary placed in the cervical canal by different physicians, we drew the obvious conclusions that such intracervical pessaries are both available to and recommended by these several physicians. In view of our experiences in treating these patients, we believe that further emphasis should be placed on the condemnation of the injudicious practice of employing such indwelling pessaries as contraceptives. To that end, the case histories of the three patients are herewith detailed briefly:

CASE 1.—Mrs. J. P. C., 30-year-old white woman, para i, was first seen on Oct. 10, 1944, in the gynecologic outpatient clinic of the ASF Regional Hospital, Fort Jackson, South Carolina. She complained of an abundant, yellowish, vaginal discharge which had appeared approximately three weeks earlier. She stated that a contraceptive device had been inserted "in the opening of the womb" on Sept. 1, 1944, by a physician in South Dakota, who had advised her to return in three months for examination. An expected menstruation, on September 20, had been abnormally profuse and had been followed by the persistent leucorrhea. Examination disclosed the presence of a rubber-covered, intracervical pessary of the wishbone variety (Fig. 1), the removal of which was followed by the escape of a large amount of foul-smelling mucus. Aside from the acute endocervicitis, no other abnormalities were noted. A smear and a culture of the cervical secretion failed to reveal gonococci. Two weeks later, the patient was relatively free from leucorrhea, and the endocervical mucus was thinner and less purulent. The patient moved to another state and was not seen again.

\*Presented at a meeting of the Philadelphia Obstetrical Society, Oct. 3, 1946.



The cerebrospinal fluid was normal six days after onset of the illness and seven days after delivery. The subsequent course was uneventful, and the patient was completely well at discharge on the tenth postpartum day.

### Discussion

The course of this patient immediately raised these questions: (1) What happens to the spinal fluid after routine caudal anesthesia? (2) How did this patient develop meningitis after an extradural invasion?

The first question was answered by the performance of lumbar puncture on each of three selected women, twenty-four hours after conclusion of caudal anesthesia continued for more than six hours. The spinal fluid was grossly and microscopically normal in each instance. Although three is a small number, the uniformity of negative result indicates that organisms do not readily contaminate spinal fluid after caudal anesthesia. Moreover, there was no suggestion of irritation of the meninges in any of these three patients.

The second question involves several others. It is reasonably certain the original anesthetic did not penetrate the patient's dura, since there was never the slightest indication of development of spinal anesthesia.

The possibility that the patient entered the hospital during the incubation stage of meningitis cannot be denied. Nevertheless, she seemed to be normal on admission, and at no time was there any suggestion of an infectious focus elsewhere in the body, despite repeated physical and laboratory examination.

There is evidence that meningitis can follow caudal anesthesia. Manalan<sup>1</sup> reported staphylococcus meningitis appearing three days after caudal anesthesia administered by silk catheter technique. His patient recovered after a severe illness. Hodges<sup>2</sup> patient received 740 c.c. of fluid during thirty-six hours, and complained of severe neck and shoulder pain with each injection during the last six hours. Later, she developed signs of meningeal irritation, but lumbar puncture was not done. Presumably the pain in this instance resulted from mechanical overdilatation of the bony spinal canal. Kremer<sup>3</sup> reported seven cases of meningitis after subarachnoid injection of anesthetic drugs, but was unable to cultivate organisms in all seven patients. He believes this is not incompatible with infectious origin, since cultivation of organisms is sometimes impossible with meningitis following open wounds of the brain.

Finally, Strong and Elwyn<sup>4</sup> point out that, "the arachnoid extends a distance along the cerebrospinal nerve roots and here the subarachnoid space becomes continuous with the tissue spaces of the nerve sheaths which in turn communicate with lymphatics."

### Summary

Clinical signs and symptoms of acute meningitis developed twenty-four hours after cessation of caudal anesthesia continued for nearly six hours in a previously normal gravida iii in premature labor. No evidence of infectious focus could be demonstrated elsewhere in the body. The spinal fluid of three selected normal patients, each carried for more than six hours on continuous caudal anesthesia, was grossly and microscopically normal. This suggests that neither metyaine nor the plastic catheter was irritating to the meninges of these three patients. This is one of the few, and perhaps the second, case of meningitis reported following continuous caudal anesthesia.

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The patient remained afebrile for forty-eight hours but, on the fifth day of hospitalization, the temperature rose to 101° F. and she complained of generalized aching, mild abdominal pain, and vomiting. Re-examination showed definite subsidence of the previously noted pelvic inflammation. Repeated blood smears for malaria, blood culture, and complete typhoid-dysentery agglutinations were all negative. However, on the seventh day, the heterophile antibody reaction was positive in a suggestive range of 1:65, and the leucocyte count was 12,000 with 90 per cent of lymphocytes.

A week later, the suspected complication of infectious mononucleosis was confirmed by finding the titer of heterophile antibodies increased to 1:112. By that time, however, the patient was again afebrile and free from symptoms. She was discharged after twenty days of hospitalization. Pelvic examination of the patient three months later disclosed no abnormalities other than a moderate endocervicitis; her blood count was normal.

CASE 3.—Mrs. W. F. M., 20-year-old white woman, para i, was admitted to the gynecologic ward of the ASF Regional Hospital, Fort Jackson, South Carolina, on Nov. 11, 1944, complaining of severe abdominal pain, nausea, and vomiting of forty-eight hours' duration. The patient stated that an intra-cervical contraceptive device had been inserted by a physician in Nebraska on Oct. 8, 1944. She had experienced a timely, though unusually profuse, menstruation on October 15. The onset of her present illness had been sudden, and had coincided with the beginning of the November period.

On admission, the patient was critically ill. She exhibited an extremely pinched facies, marked dehydration, and cyanosis. The temperature, pulse, and respirations were 104° F., 110, and 28, respectively, and the blood pressure was 96/50. The abdomen was grossly distended, markedly rigid, "silent," extremely tender, and showed rebound pain in all quadrants. A rubber-covered, stem pessary of the wishbone type was removed from the cervical canal, whereupon 5 c.c. of malodorous, sanguineous fluid escaped. The uterus, though normal in all details, could not be manipulated without eliciting severe pain. There were no other pelvic abnormalities. The laboratory data included the findings of a leucocytosis of 28,000 with 88 per cent of polymorphonuclear cells, no anemia, negative serology, and the absence of gonococci in both smear and culture of the cervical secretion. A diagnosis of generalized peritonitis, secondary to metritis and parametritis, was made, and penicillin therapy was instituted.

The patient was given an initial dose of 100,000 units of sodium penicillin intravenously and, thereafter, 20,000 units intramuscularly every three hours. Her critical condition, however, persisted. On the third day of hospitalization, pelvic examination revealed an accumulation in the cul-de-sac. A colpotomy was performed, releasing 240 c.c. of foul-odored pus. The patient improved immediately, and the temperature fell to normal by lysis during the course of a week. Penicillin therapy was discontinued on the tenth day of treatment, a total of 1,700,000 units having been administered. After six weeks the patient was discharged in good condition, showing only slight residual thickening of the cul-de-sac. Recovery must have been fairly complete, for a year later information was received that she was in her sixth month of gestation.

### Summary

The dangers inherent in the presently available devices designed to give more permanent contraception than is offered by the safer, though less permanent, means are too little appreciated by many physicians. Within a period of four weeks, the authors treated three patients who exhibited varying degrees of

CASE 2.—Mrs. L. M., 22-year-old white woman, para i, was admitted to the gynecologic ward of the ASF Regional Hospital, Fort Jackson, South Carolina, on Nov. 1, 1944, complaining of chills, fever, and abdominal pain. She stated that a physician in Colorado had inserted "a rubber button in the womb" for the purpose of prolonged contraception on Sept. 10, 1944, and had advised her to return for examination in three months. Since then, the patient had experienced three attacks of menometrorrhagia, each from ten to fourteen days in duration, and had acquired a thick, yellowish leucorrhea. Four days prior to admission, while en route by train from Colorado to South Carolina, she began to suffer severe pain in the lower abdomen, vomiting, chills, and fever.

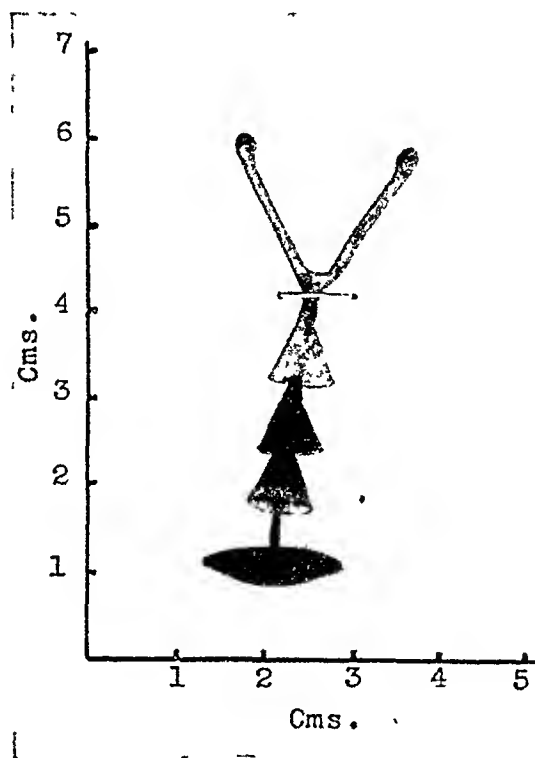


Fig. 1.—Latex-covered, reverse-valve type of intracervical pessary employed as a means of attaining prolonged contraception. Note the dangerous springlike intrauterine portion.

On admission, the patient was obviously very ill. The temperature, pulse, and respirations were 103° F., 110, and 20, respectively, and the blood pressure 98/54. Dehydration was evident. The abdomen was tense, moderately distended, tender to pressure in the lower half, and exhibited pain on rebound in the left lower quadrant. A rubber-covered, stem pessary of the wishbone type (Fig. 1) was removed from the cervical canal, permitting the escape of a small quantity of malodorous mucus. Pelvic tenderness was extreme, the uterus was fixed in second degree retroversion, and both parametria were thickened. The cul-de-sac, however, was empty, and neither adnexus was palpable. A smear and a culture of the cervical secretion showed no gonococci. The admission leucocyte count was 4,750 with 68 per cent of lymphocytes, the urinalysis was normal, and the serology was negative.

Sulfadiazine in full oral dosage, from 8 to 10 Gm. per twenty-four hours, and fluids intravenously were initiated shortly after the patient's admission. On the third day, the patient was comfortable and afebrile, but the leucocyte count was 4,000 with 78 per cent of lymphocytes. The sulfadiazine was discontinued.

## DYSGERMINOMA AND PREGNANCY

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UP TO date, about 300 cases of dysgerminoma have been reported. It is thus evident that this type of ovarian tumor is comparatively uncommon. A large number of these 300 cases, especially the ones that were reported early, had been associated either with pseudohermaphrodisism or underdevelopment of the gonads. While dysgerminoma is the most common tumor found in pseudohermaphrodites, it is now believed to occur more commonly in women with normal genitals. Since 1938 this fact has been emphasized by Miller, Novak,<sup>9</sup> and Selye.<sup>10</sup> They have also verified the fact that dysgerminomas do not alter the hormonal or gonadal status of the female and have occurred with pregnancy.

The number of cases of dysgerminoma operated upon during pregnancy are very small. Several authors have reported isolated cases. One of us (M. V.) reported a case of dysgerminoma which was removed in the third month of pregnancy. The patient was subsequently delivered of a living baby. It is now five years since the removal of the tumor and the patient has had a second child. She is in excellent health. In 1940, Nyst<sup>1</sup> recorded a case of dysgerminoma complicating pregnancy. The tumor mass lodged in the cul-de-sac and prevented descent of the head. A cesarean section was performed and the right adnexa removed. Abernethy,<sup>2</sup> in 1943, reported a pregnancy complicated by dysgerminoma. The latter also was lodged in the cul-de-sac. After forty-eight hours of labor, a cesarean section was done and a stillborn baby was delivered. Due to the poor condition of the patient, the ovarian tumor was left in situ and three months later a right oöphorectomy was performed. The pathologic report was dysgerminoma. Another case of removal of dysgerminoma during pregnancy occurred at Beth Israel Hospital, New York City, in 1944.

In the cases where pregnancy complicated the presence of a dysgerminoma, there were no evidences of any abnormality of the genitals. Our case also emphasizes this point.

### Report of Case

A well-developed and well-nourished young woman (E. C.), aged 23 years, gravida ii, para i, on her present admission to the hospital July 23, 1945, complained of lower abdominal pain. Her past history revealed that in 1943 she was delivered of a 6½-pound living child by low forceps and mediolateral episiotomy at the hospital. Two hours after delivery the patient went into shock, her blood pressure dropped to 90/60. There were no external signs of bleeding; her pulse was 120; no air hunger was apparent, but the patient complained of severe abdominal pain. Her lower abdomen was rigid. A diagnosis of twisted ovarian cyst was made. One thousand cubic centimeters of 5 per cent glucose in saline were administered, and patient's general appearance improved rapidly. Her blood pressure rose to 110/60; and her pulse slowed down to 100. The blood count now was 3,800,000 red blood cells, 68 per cent hemoglobin, 14,000 white blood cells. Pain gradually subsided, and in forty-eight hours the patient recovered from the attack. On the tenth postpartum day she was discharged. Vaginal examination at this time revealed a semisolid mass 13 by 12 by 6 cm. in the region of the left ovary. The uterus was anterior and well involuted. Right adnexa were negative. The perineum was well healed.

pelvic inflammation initiated by a wishbone type of intracervical pessary which had been inserted to effect long-lasting contraception. Within eight weeks after the introduction of the pessary, one of the three women had developed severe endocervicitis, another suffered from acute parametritis complicated by infectious mononucleosis, and the third patient was critically ill with generalized peritonitis. The interesting fact that all three patients had emigrated from the same section of the United States within a few weeks of each other suggested both the ready availability of the intracervical pessary in that locale and the willingness of physicians to insert it. Physicians, perhaps, assume that the sale of such items by surgical supply companies constitutes somehow an endorsement of their safety and value. The authors emphasize that such devices are dangerous and should be withdrawn from the market.

2116 SPRUCE STREET  
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The patient returned in six weeks, and vaginal examination was similar to that on day of discharge. She was advised to have an oöphorectomy six months later, unless an acute episode should occur in the interim.

However, in December, 1944, about two years after the birth of her child, the patient was seen again and she now gave a history of two months' amenorrhea. Her last period had occurred Oct. 24, 1944. She had had no complaints or attacks in the past two years. Except for all the signs of early gestation, and a mass 13 by 12 by 6 cm. in the left adnexal region, freely movable, the patient was in excellent health. Throughout the antepartum period the urine and blood pressure were essentially normal.

On July 15, 1945, about two weeks before the expected date of delivery, examination revealed the ovarian mass which had previously been freely movable, was now fixed in the pelvis and could not be dislodged. A cesarean section was advised. On July 24, 1945, under general anesthesia, a Monro-Kerr low flap operation was performed. A living 6 lb., 6 oz. male infant was delivered. At the same time a left salpingo-oöphorectomy was performed. The tumor mass that was present since 1943 was removed. A Pomeroy sterilization was done on the right tube. The pathologic report of the specimen removed from the left ovarian fossa was as follows:

*Gross:* An irregular ovoid capsulated tumor 13 by 12.5 by 6 cm. was present. The capsule was intact. Cut surface of the mass showed homogeneously pale, greyish purple areas without markings. Some necrosis was present in the center. The picture is suggestive of dysgerminoma.

*Microscopic:* Section of this tumor revealed a collection of large cells with vesicular hyperchromatic round nuclei. The cytoplasm was scanty and was faintly stained. Mitotic figures were seen throughout. The cells were arranged in small alveoli. Stroma was scant. The trabeculae were made up of loose, edematous poorly vascularized connective tissue. There is a mild lymphocytic infiltration.

Her postoperative course was uneventful, and she left the hospital on Aug. 5, 1945, twelve days after the section. The patient returned every three months for follow-up examinations, and on three successive visits the vaginal examinations have been essentially negative. Observation is to be continued.

### Comment

From this case and others mentioned, it should be clear that the concept that dysgerminoma is mainly associated with pseudohermaphroditism and hypoplasia of genitals is no longer tenable. It may be complicated by pregnancy in individuals with perfectly normal genitals. Pregnancy occurs more often than is thought in cases of dysgerminoma.

Where the dysgerminoma is unilateral and well encapsulated, conservative surgery has proved successful. This is important, especially since these tumors occur in comparatively young women. It is felt that dysgerminoma is not as malignant as previously considered.

On all cases reported in the literature, the diagnosis of dysgerminoma was made only by the pathologist. It is important to think of this condition at the operating table so that the proper type of operation may be chosen.

### Summary

Pregnancies before and after removal of dysgerminoma have been reported, but removal of the tumor during pregnancy is rare. The case herein reported showed a woman with dysgerminoma delivered of a living baby by low forceps and episiotomy, who went into shock two hours later, recovered, and went home

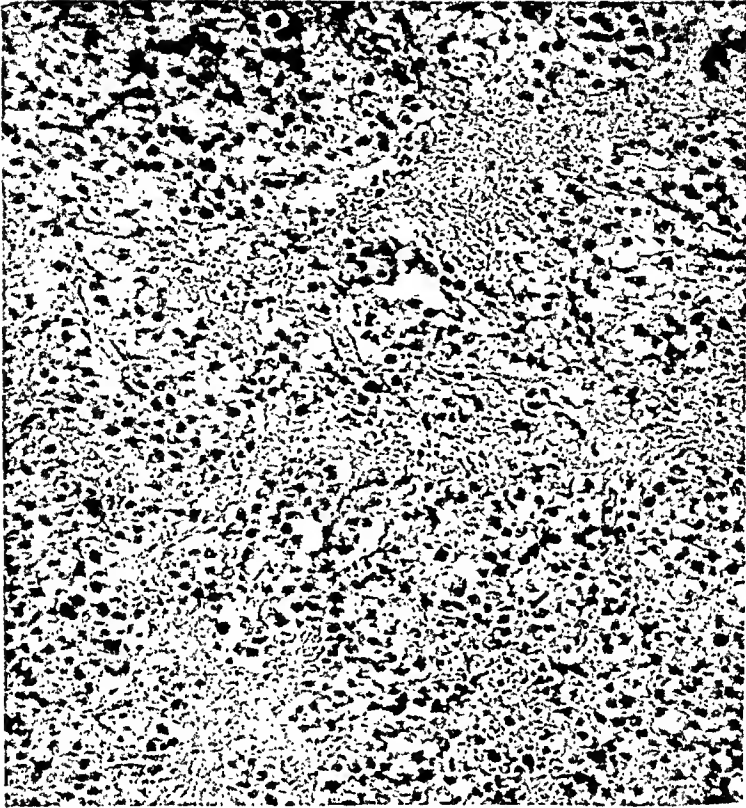


Fig. 1.—Section of tumor, low power.

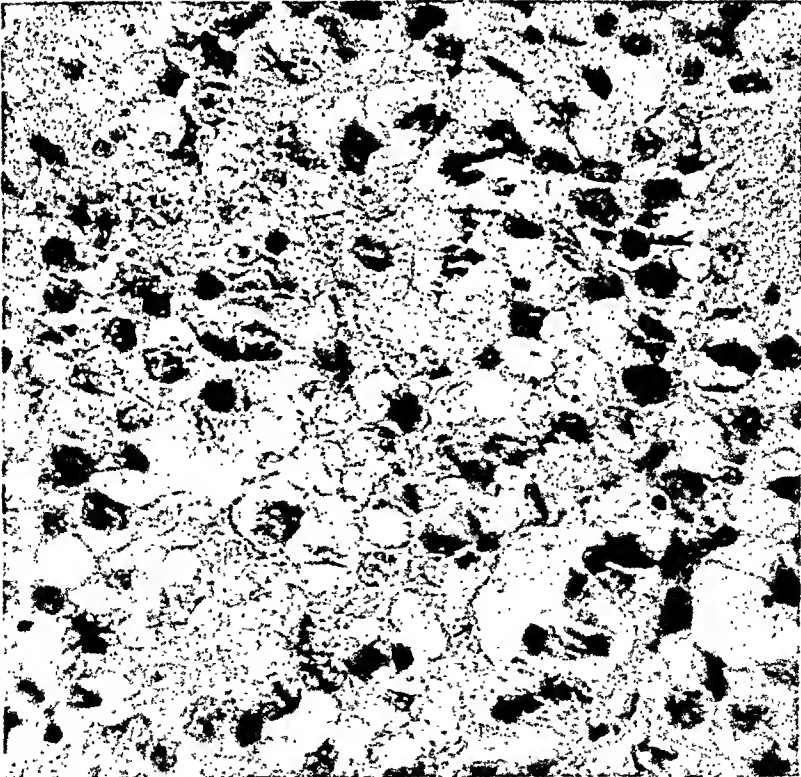


Fig. 2.—Same section, high power.

# BILATERAL DERMOID CYSTS, UTERINE FIBROIDS, AND PREGNANCY

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**A** DESCRIPTION of the following case is believed warranted by the rarity of its pathology.

M. S., primigravida, aged 27 years, white, amenorrheic for three months, complained of the following signs and symptoms: continuous and severe pain in the right and left lower abdominal quadrants, incontinence, and progressive enlargement of the abdomen to the size of a 7 months' pregnancy. This growth took place over a period of eighteen months. During the last three days, the patient experienced what appeared like "menstrual cramps," with the passage of large blood clots. Previous history—menstrual, medical, and surgical—was essentially negative.



Fig. 1.

General examination was negative. Abdominal palpation revealed an exceedingly hard mass, rounded and regular, in the midline of the abdomen, extending from the symphysis pubis to 5 cm. above the umbilicus. Tenderness was elicited over the mass as well as in both lower lateral quadrants. There was no rigidity. On vaginal examination the cervix was found soft, and two firm masses were palpated filling up the lateral fornices, with a soft, boggy mass felt in the posterior fornix. The impression was that of a single massive fibroid of the fundus, with pedunculated fibroids or ovarian cysts in the lower quadrants, associated with an intrauterine pregnancy situated in the hollow of the sacrum. Red degeneration of the fibroid suggested itself. Due to the complaint of severe pain, a laparotomy was decided upon.

Under fractional spinal anesthesia the abdomen was opened in the midline. The findings were: single, massive, fundal fibroid, bilateral dermoid cysts the



ten days later. Two years later she became pregnant again and had a cesarean section due to the fact that this time the dysgerminoma blocked the descent of the head. At the same time the ovarian tumor was removed, and on pathologic examination proved to be a dysgerminoma.

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## SUCCESSFUL REPAIR OF A VESICOVAGINAL FISTULA COMPLICATING CARCINOMA OF THE CERVIX

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THE appearance of a vesicovaginal or rectovaginal fistula in a patient with carcinoma of the cervix usually means that the tumor has spread so extensively that little hope for a permanent cure can be expected. The following case, however, is a good example of the wisdom of the axiom "while there is life there is hope."

Mrs. J. M., a 58-year-old, para i, was first seen on Dec. 22, 1941, because of weakness and bloody vaginal discharge. Examination revealed a large cauliflower-like mass originating in the cervix and filling the upper vagina. In addition there was moderate infiltration of the parametria.

The patient was hospitalized, given a transfusion of 500 c.c. of blood and protracted deep x-ray therapy. A total of 4,000 r. were given in 20 divided doses through four portals using a 200 kilovolt source at 20 cm. distance with 1 mm. of copper and 1 mm. aluminum filtration. There was considerable regression of the tumor during and following the deep x-ray therapy. Consequently the patient was readmitted to the hospital on Feb. 24, 1942, for implantation of radium. Examination at this time showed a vesicovaginal fistula 1.5 cm. in diameter about 2 cm. anterior to the cervix in the midline. Despite the apparent futility of additional therapy, radium was implanted in the hope that it might be beneficial. Three capsules each containing 25 mg. were placed in tandems in a brass container and inserted in the cervical canal. In addition, a 25 mg. capsule was placed in sponge rubber and inserted in the upper vagina against the cervix. The radium was removed after twenty-five hours, giving a total dose of 2,500 mg. hours.

For the next two and one-half years the patient was seen periodically at her home. As time elapsed it became more and more apparent that the tumor had been successfully eradicated and that eventually an attempt should be made to repair the fistula. Consequently, she was hospitalized for the third time on Oct. 10, 1944. Under nitrous oxide-oxygen and ether anesthesia, the fistula was closed. The opening was about 1 cm. in diameter and surrounded by dense scar tissue. The edges were excised, the surrounding tissue mobilized, and the bladder closed with a continuous suture of 0-20 mg. chromic catgut. Sulfathiazole powder was applied to the area and the vaginal mucosa closed with a similar suture.

The vagina was tightly packed with gauze and a retention catheter inserted. The postoperative course was uneventful. After the catheter was removed on the tenth day, the patient had good control of the urine, although there was moderate frequency due to small bladder capacity. The bladder capacity has gradually increased and the fistula has remained closed now for one and one-half years.

This patient is of interest because of the spontaneous appearance of a vesicovaginal fistula during deep x-ray therapy for carcinoma of the cervix, the achievement of a four and one-half year cure by the use of x-ray and radium therapy in an apparently hopeless case, and the successful closure of a vesicovaginal fistula following radiation.

size of small grapefruits, and an intrauterine gestation of ten weeks' duration situated at the base of the fibroid and encompassed by it above and at the sides. A supracervical hysterectomy and bilateral oöphorectomy were performed; myomectomy plus ovarian cystectomy, ideally a procedure of choice, was considered, but deemed impossible in this particular case.

The pathologic report confirmed the clinical findings, namely, bilateral dermoid cysts, filled with black hair—the color of the mother's—and thick, yellow caseous material, fibromyomata uteri showing red degeneration, and a fetus of ten weeks.

### Summary

A case is reported of a ten weeks' gestation, associated with a single massive fibroid of the fundus and bilateral dermoid cysts, in a 27-year-old, white primi-gravida. Treatment consisted of hysterectomy with bilateral oöphorectomy.

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and contour of the cavity were those of a normal vagina, and the walls were more like a raw membrane than loose connective tissue. Protruding from the new anterior wall was a raw nubbin of firm tissue which was found to have a short canal. This was dilated and curetted. A plug was inserted to keep the vagina open.

Microscopic examination of the curettings showed cervical glands with chronic inflammation of the stroma containing lymphocytes, circular groups of epithelioid cells, and a few giant cells. Acid-fast stain showed no Koch's bacilli. Diagnosis: chronic granulomatous endocervicitis, probably tuberculosis.

X-ray films of the chest and abdomen showed no evidence of pathologic process. Intravenous pyelograms, obtained later, were likewise negative. It is unfortunate that no guinea pig inoculations of urine, or the cervical curettings were obtained.

In view of probable tuberculosis of the tubes as well as the uterus, it was decided to operate upon this patient.

Four days later the abdomen was opened and a small uterus along with both tubes and the left ovary were removed without incident. No tubercles were found on the peritoneum. The uterus was free of adhesions, but adnexal structures on both sides were matted together with dense adhesions. Both tubes were thickened and nodular, the left more than the right. Neither bowel, bladder, nor any other organ was adherent or nodular. When freed of adhesions, the right ovary, which was left in the abdomen, appeared normal. The left ovary contained a hemorrhagic corpus luteum.

Microscopic examination of these organs showed typical tubercles with central areas of necrosis, epithelioid cells, and Langhans giant cells in the left tube. Similar, though less frequent, tubercles were found in the uterus, which was completely lined with fibrinopurulent exudate. No endometrium could be found. Only a rare, small tubercle was present in the cervix. The ovary contained a corpus luteum cyst and was free of cellular infiltration.

The postoperative course was uncomplicated except for moderate temperature elevation and pyuria, due to cystitis, which began on the fourth postoperative day. This responded promptly to a short course of sulfathiazole. Her urine remained clear thereafter. There was no pulmonary or gastrointestinal complication.

Before the panhysterectomy, the glass plug was removed from the vagina and it was replaced with an iodoform packing. This was removed on the third postoperative day, and there was no more than the usual amount of vaginal discharge. On the eighteenth day after panhysterectomy the vagina was examined under anesthesia. The newly opened portion of the vagina was surprisingly clean and smooth, and apparently, covered with young epithelium. No sign of infection or ulceration was present. The vault closure was healing well and remained well suspended. Several biopsies were taken from different portions of the vagina. Microscopic examination showed squamous epithelium, some of it young, with fibroblasts and numerous capillaries. There were scattered lymphocytes, large mononuclear cells, and Langhans giant cells, but no typical tubercles.

The vagina continued to heal well, and the patient was discharged on the twenty-first day after the panhysterectomy in good condition.

Several months after leaving the hospital, the patient was married, and reported normal marital relations satisfactory to both herself and her husband. At that time the vagina was well epithelialized and elastic, except for the innermost two or three centimeters which remained raw and granulating. This gradually constricted until now, two years later, it forms a blind, raw, cul-de-sac

## GENITAL TUBERCULOSIS WITH ATRESIA OF THE VAGINA AND AMENORRHEA

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THE case presented here is of interest not only because of the rarity of vaginal tuberculosis, but it is believed to be unique in that it was accompanied by atresia of the vagina and complete amenorrhea simulating congenital aplasia of the genital organs.

C. P., a 19-year-old single Negro woman, presented herself in the dispensary because she had never menstruated. She also confided that she was planning to marry and that her vagina was inadequate. On questioning, she told of dizziness, headache, and nosebleed which seemed to occur at monthly intervals, but this was not constant. She had had a thick, yellow, malodorous vaginal discharge for many years. Otherwise she had always been in good health and had felt well all her life, her only previous illnesses being those usual to childhood.

There was no family history of tuberculosis or anything suggestive of endocrine dystrophy.

Examination showed her to be a normally developed and well-nourished 19-year-old Negro woman with a mature, feminine figure, and normal secondary sex characteristics. The temperature, pulse, respirations, and blood pressure were normal. No lymph nodes were palpable. The thyroid was diffusely enlarged to about twice normal size and was moderately firm. No bruit was heard. The chest was normal to percussion and auscultation. The heart was percussed within normal limits, but a blowing systolic murmur, thought to be functional, was heard over the base. There was normal breast development, and a female escutcheon. The abdomen was flat, showed no sign of tenderness, rigidity, or palpable organs or masses. The remainder of the general examination was negative.

Pelvic examination revealed normal external genitals, Bartholin's and Skene's glands. The outlet admitted two fingers, but the vagina ended in a blind cul-de-sac, was about 3 cm. deep, and was lined with normal, healthy looking mucosa. No cervix was seen or felt, and no uterus was palpable by the vaginal route. However, on rectal examination a small, firm, elongated mass was felt above the vagina and was adjudged to be the uterus.

*Laboratory findings.*—Hemoglobin, 75 per cent, red blood cells, 4,000,000, white blood cells, 4,300. Voided urine showed 15 to 20 white blood cells per high power field, no albumin or sugar, sp.gr. 1.027. Microscopic precipitation test was negative. Blood sedimentation curve was normal.

It was thought that the patient had congenital atresia of the vagina without evidence of glandular disorder.

Since the patient's primary concern was to acquire an adequate vagina, construction of an artificial vagina by the Wharton technique was planned. Under anesthesia, a pin-point opening surrounded by a small area of erosion was found in the apex of the abbreviated vagina. A fine probe could be passed into the opening for one-half inch, and several drops of mucoid material exuded from it. The vault was incised to either side of the sinus, an easy plane of separation was found, and, without difficulty, a normal-sized vagina canal was opened. The size

in numerous sections of the uterus. The patient was always considered to be in excellent health, so general debility could not be counted as playing a part. It is also to be noted that normal, nontuberculous ovaries were found, one bearing a corpus luteum. No atretic follicles were present. These findings argue against any endocrine disturbance.

The atresia of the vagina appears to be unique for, although acquired strictures have been reported as resulting from trauma, chemical burn, and infections such as gonorrhea and chancroid,<sup>10-12</sup> none has previously been attributed to tuberculosis. It may be pointed out that the vaginal vault, which had previously been adherent and granulomatous, healed readily when separated and exposed. A similar case was reported by Labhard,<sup>13</sup> in which the thickened mucosa removed during a plastic procedure for procidentia was found to be tuberculous. The repair healed promptly, and there was no sign of complication six years later. In most of the reports examined by Wharton, the lesions were relatively superficial ulcers, chronic and indolent, showing little inclination to spread. This lends support to the idea that the vagina has a high degree of resistance to the disease.

The only significant symptoms, in addition to amenorrhea and atresia, was the yellow, malodorous discharge, which is the most common symptom attributable to tuberculosis of the lower genital tract alone. Usually the more prominent symptoms are those due to general phthisis or to actively advancing disease of the upper genital tract, neither of which were present in our case. The chronic, almost quiescent, course of this patient draws attention to the fact that pelvic tuberculosis can be, and frequently is, a localized and indolent disease with few signs to focus attention to it.

The question might rightly be asked, in view of the fact that the patient remained in good health with no sign of extension for at least six years, why surgical intervention was felt necessary. It should be pointed out that, in spite of the benign course of the lesion, the infection remained active, showing focal necrosis and producing purulent discharge for at least six years also. Knowing the characteristic tendency of tuberculosis to recur and extend even after years of quiescence, it was reasonable to fear that event in this case. Actually, an unusual opportunity was presented: that of removing the only known focus. It was necessary to leave the vault of the vagina in order to preserve a functioning organ, but since this was a relatively superficial lesion, probably kept alive by the more deeply seated infection above, this hazard was not considered to be too great. As it turned out, the apex of the vaginal vault did become constricted, and still occasionally drains a small amount of mucopurulent material, but the area involved is minimal and shows no sign of extension. It is hoped that this will ultimately heal. Despite the constriction of the apex, the vagina is adequate and functions satisfactorily.

### Summary and Conclusions

1. A case of genital tuberculosis involving the vagina and simulating congenital aplasia of the generative organs is presented.
2. Our incidence of 2.47 per cent vaginal tuberculosis conforms with recent reports in the literature.
3. The infection of the vagina is construed to be secondary. Other so-called primary cases have been similar and may have been secondary invasions.
4. The rarity of vaginal tuberculosis may be explained by the resistance of the mature vaginal mucosa.
5. Complete amenorrhea was perhaps due to total obliteration of the endometrium.

which barely admits the tip of the finger. The adequate portion of the vagina is seven centimeters deep and functions well. Recent intravenous pyelograms and chest films are negative, and the patient enjoys a healthy, vigorous life.

### Discussion

The above case was only the second instance of vaginal tuberculosis seen at University Hospitals in the past twenty-five years. During this time a total of 81 cases of genital tract tuberculosis have been treated, giving an incidence of 2.47 per cent. Friedlaender<sup>1</sup> contributed the first case to the literature in 1875, and as late as 1925, Wharton<sup>2</sup> estimated that a total of no more than 75 cases had been reported. Stevenson<sup>3</sup> calculated from the literature an average incidence of 0.5 per cent but, subsequently, Auerbach<sup>4</sup> and Eichner<sup>5</sup> have reported two series of cases showing an incidence of 3.1 per cent and 3.8 per cent, respectively. It becomes apparent that the diagnosis is being made more often.

An adequate discussion of our only other case cannot be included in this paper; however, it may be pointed out that the case was one of generalized tuberculosis which went to autopsy. It teaches a most significant lesson, because six years prior to the time when the diagnosis was made, the patient had had a unilateral salpingo-oophorectomy at another hospital for "pelvic inflammatory disease." Tuberculosis was apparently present at that time, for a draining sinus developed in the wound and did not heal for six months. This same sinus was found at the autopsy and was tuberculous.

It has long been debated whether the vagina and cervix may be the site of primary infection, and some reports of so-called primary lesions have appeared in the literature.<sup>1, 2, 7</sup> It is to be noted, however, that few represented the only lesion found at autopsy or operation. The consensus of opinion is that a primary lesion is rarely, if ever, found in the vagina. Our case demonstrates the kind which is frequently assumed to be primary, for no other clinical lesion can be found elsewhere than in the genitals. However, it will be observed that the more abundant and apparently older tubercles were found in the oviducts, and that they became progressively fewer and smaller in the corpus, cervix, and vagina. This suggests that the infection originated in the oviduct and progressed by direct extension to the remainder of the genitals. Since our inability to find another lesion elsewhere does not rule out the hematogenous route of infection, we must assume that the vaginal involvement was secondary, as is suggested by the pathologic findings, i.e., blood-borne from an obscure primary lesion to the tubes and thence, by direct extension, to the remainder of the genitals.

Novak<sup>8</sup> has pointed out that the rarity of vaginal tuberculosis may be explained by the high resistance of the mature vaginal mucosa which is much more like skin than mucous membrane. It would reasonably follow then, that the infantile vagina might be more susceptible, just as it is to gonorrhea. This speculation is supported by the age incidences reported by Wharton, who found twice as many cases occurring in the years before ten, as in any other decade of life. Obviously, our case was acquired before puberty, and it seems doubtful that the vagina would have become involved had the purulent discharge from the uterus bathed a more resistant mature vaginal mucosa.

The amenorrhea is of interest, not only because it had persisted for six years beyond the usual age of puberty, but because the cause can be fairly definitely established. Amenorrhea has been reported<sup>9</sup> as occurring in 27 per cent of genital tuberculosis, while the other menstrual disturbances are said to occur in as high as 75 per cent.<sup>6</sup> The cause has variously been attributed to general phthisis, hyper- or hypo-ovarianism, and mechanical interference with the endometrium. The latter is the probable cause of this case, for the endometrium was completely replaced with fibrinopurulent exudate, no glands being found

## CO-EXISTING DIFFERENT TUMORS OF THE OVARIES

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THE investigation of the embryologic and pathologic origins of certain ovarian tumors has not progressed beyond the hypothetical or conjectural stage.

It is well known that dermoid cysts of the ovary contain a variety of macroscopic and microscopic elements, and in a large series of 225 cases of dermoid cysts, Blackwell and co-workers<sup>1</sup> observed 32 different tissue varieties. This would indicate more than a coincidental common origin and misplacement and invasion of strayed, different tissues is very much in evidence. In endometriomas there is also a large degree of misplacement according to Sampson,<sup>2</sup> yet Novak<sup>3</sup> claims that perhaps the ovary may be the point of origin for the implantation of endometrial tissue. Siegler<sup>4</sup> mentions endometriosis in the ovary as a manifestation of faulty ovarian secretion with estrogen chiefly responsible for the subsequent sclerosis of the ovary.

We present the following case of a dermoid cyst in one ovary occurring simultaneously with an endometrial cyst of the other ovary in a woman who previously had a pilonidal cyst removed, in an attempt to enhance the theories of ectopic origins in pathologic entities such as these.

The occurrence of dermoid cysts of the ovary is reputed by Novak<sup>5</sup> to be 10 per cent of all cystic neoplasms of the ovary. Of this, 25 per cent occurs bilaterally. Bernstein<sup>6</sup> found a somewhat higher incidence, 16 per cent, in 1,101 gynecologic patients, but makes no mention of co-existing lesions. His figures for endometrial tumors of the ovary show a 4 per cent incidence. In combination with other lesions, Blackwell and co-workers<sup>1</sup> found only three cases of dermoid cysts of the ovaries associated with endometriosis in their series of 225 cases, although one may presume that these were generalized endometriosis. They do not mention any organ specificity of the endometrial involvement in the cases where the dermoid cysts were found. It is with interest then that we present this infrequently occurring combination of ovarian tumors.

Mrs. P. S., white, aged 35 years, was admitted to the Unity Hospital, Brooklyn, N. Y., on Jan. 4, 1946, and was discharged Jan. 18, 1946. Her complaints were of pains in both lower quadrants of the abdomen which were dull and steady since the birth of her first child ten years prior to admission. Of significance in the past history, which otherwise was entirely negative, was the fact that she had a pilonidal cyst removed in 1935. Obstetrically, Mrs. P. S. had had two children, one in 1934, a 4 lb. premature infant, and a child of normal weight in 1940, both of which were delivered with forceps. Her periods started at the age of 12 years, recurred cyclically every twenty-eight days, and lasted for five days. At no time did she have menorrhagia, metrorrhagia, or dysmenorrhea.

Examination was normal except for gynecologic findings. The introitus was multiparously relaxed, the cervix was lacerated, eroded and cystic, tender on motion, and pointed upward; the uterus was retroverted, fixed, and tender, and there was a fullness in the left fornix. The adnexa were tender but were not palpable.



6. The vaginal lesion, resulting in atresia, was a superficial ulcer. This is the most common tuberculosis lesion seen in the vagina, but no other instance of resulting atresia is known.

7. Vaginal discharge and amenorrhea were the only symptoms. This illustrates the indolent and apparently benign course genital tuberculosis frequently follows.

8. Surgical treatment removed the main focus of infection, and provided the patient with a functioning vagina.

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fibrillar keratin. A second section showed a markedly thickened segment of cyst wall made up of hypertrophic sebaceous glands (Fig. 2). These glands were continuous with the flat, stratified, epithelial tissue forming the cyst wall proper. A third section showed an inner epithelial membranous tissue with development of folds of villi. Some of the villi showed markedly vacuolated squamous epithelial cells at the tip. There was submucous fibrillar connective tissue which, in turn, rested upon a muscular layer. There were a few rather well-developed glands lined with cylindrical epithelium embedded in the submucosal connective tissue layer. A muscular layer showed well-developed muscular fascicles. The mucosa described above was continuous with thin, flat, squamous epithelium similar to that described above. Microscopic section of the ovary proper showed a large cyst lined with a thin, flat, epithelial membrane.



Fig. 3.—Endometrial gland, magnified 43 times, lined by broad cylindrical epithelium and surrounded by darkly stained stromal cells with little or no cytoplasm.

This membrane rested upon a markedly hypertrophic, fibroblastic tissue layer which showed old blood pigment in the interstices. There was another area in this section which showed a glandlike structure consisting of tall and broad cylindrical epithelium. This gland was surrounded by loose, hypertrophic, and fibroblastic tissue which showed hemorrhagic extravasation, fibrosis at the periphery, and old blood pigmentation (Fig. 3). Another section of the mass showed fetal cartilage embedded in differentiated fat tissue. Final diagnosis: follicular cyst; endometrial chocolate cyst; dermoid cyst with teratomatous tissue elements.

### Discussion

The existing theories for the origin of dermoid cysts in the ovary are not conclusive. The parthenogenetic theory which holds that the teratoids arise from unfertilized ova or as a result of cleavage in unfertilized but mature ova is doubtful, since it is unlikely that ova can form teratoids of a complex nature (Selye<sup>7</sup>). The blastomere theory of Bonnet<sup>8</sup> and Marchand<sup>9</sup> states that the

On Jan. 5, 1946, a laparotomy was performed, and a dermoid cyst of the right ovary and a chocolate cyst of the left ovary were removed. The uterus was suspended, and a tracheloplasty and repair of a lacerated pelvic floor were done. There were endometrial implants in the posterior cul-de-sac which were cauterized.



Fig. 1.—Ovarian tumors removed at operation. Dermoid cyst (left) containing cheesy material and hair, chocolate endometrial cyst (right).

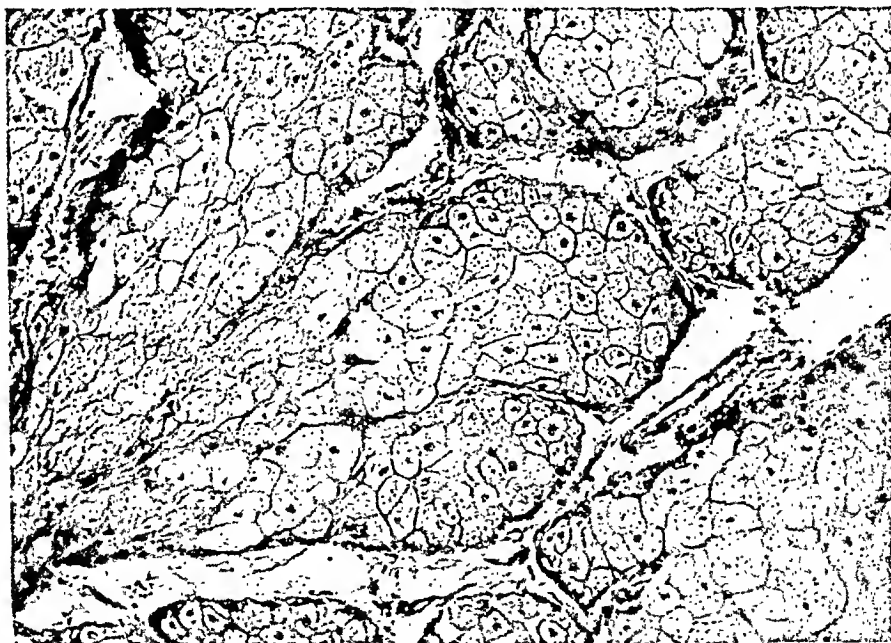


Fig. 2.—Section of dermoid cyst, magnified 180 times, showing hypertrophied sebaceous glands.

Examination of the ovarian tumors removed at operation revealed the right ovary to measure 8 by 4 by 4 cm., and the left ovary to measure 4 by 2 by 1 cm. (Fig. 1).

Microscopic sections of the ovarian tumors showed (in one section) an ovarian follicle with ovum in the center. There was also a well-developed cyst made up of granulosa cells showing dilatation and gaping. A second cyst wall showed flat and thin squamous epithelium, the inner surface of which showed

## Special Article

### THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY; A FIFTEEN-YEAR REVIEW\*

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IT WOULD appear timely that a review of the problems and results of this organization's activities be presented now that it has completed more than fifteen years of work.

In 1930 the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, the American Gynecological Society, and the Section on Obstetrics and Gynecology of the American Medical Association each elected three Fellows to constitute the American Board of Obstetrics and Gynecology.

The Board was incorporated, organized, and held its first meeting in September, 1930. At that time the By-Laws were adopted and provisions were made, by resolutions, for its proper functioning.

This Board had been in the process of organization since 1927 and put into action a determined effort on the part of these three national organizations to improve the standards of practice of obstetrics and gynecology.

The avowed purposes of the Board, still unchanged from their original wording, have been as follows:

*First:* To elevate the standards and advance the cause of obstetrics and gynecology.

*Second:* To determine the competence of practitioners professing to be specialists in obstetrics and gynecology.

*Third:* To arrange, control, and conduct examinations to test the qualifications of voluntary candidates appearing before the Board for certification as specialists in obstetrics and gynecology.

*Fourth:* To grant and issue certificates of qualification as specialists in the field of obstetrics and gynecology to candidates successful in demonstrating their proficiency.

*Fifth:* To serve the public, hospitals, and the medical schools by preparing lists of specialists certified by the Board.

These activities proceed from the certificate of incorporation in which it is stated that "the nature of the business and the objects or purposes proposed to be transacted, promoted, and carried on by it" are as follows:

"To encourage the study, improve the practice, and advance the cause of obstetrics and gynecology, subjects which should be inseparably interwoven; and to grant and to issue to physicians duly licensed by law, certificates, or other equivalent recognition of special knowledge in obstetrics and gynecology."

An unavowed but determined policy of the Board has always been that everything about its activities, its investigations and examinations of candidates, its decisions and actions taken must be conducted on a high plane of

\*Read, by invitation, before the Brooklyn Gynecological Society, Nov. 1, 1946.

†Dr. Titus has been the Secretary of the Board since its Organization, and has contributed largely to the important developments which the organization has achieved. This frank and authoritative statement is worthy of careful consideration by our readers.

The Editor.

teratoids arise from blastomeres separated from the rest of the fetal body, a theory which fails to explain the more than frequent occurrence of gonadal teratoids. In endometriosis, its occurrence is probably due to a combination of pathogenic mechanisms including implantation, regurgitation of endometrial particles, and metaplasia of oviduct mucosa, as well as metaplasia of celomic epithelium (Herd<sup>10</sup>).

The case herewith represented in which a dermoid cyst with its various tissue elements in one ovary and an endometrial cyst in the other ovary without generalized endometriosis were found in a woman previously operated upon for removal of a pilonidal cyst has stimulated us to regard the origin of cysts such as these in a different light. It is our contention from observation of this case that perhaps certain organs have an inherent ability to harbor embryonic rests and, when the individual organism reaches full maturity, these rests undergo metaplasia and appear clinically.

### Summary

1. A case of co-existing different tumors of the ovaries is presented. One was a dermoid cyst, the other an endometrial cyst in a patient with a previous history of a pilonidal cyst.
2. An attempt to explain the origin of this combination is given.
3. One should be aware of the appearance of other ectopic tumors in organisms which have already exhibited one ectopic neoplasm.

Grateful acknowledgment is given to Dr. W. E. Youland, Associate Pathologist of the Unity Hospital for the preparation and description of the specimens.

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616 EASTERN PARKWAY

go to a referee is not generally classified by candidates as being a "nerve sedative" or designed to relax their mental tensions, but many a candidate has had his ease ably and successfully pleaded for him later by his referees.

Notes are taken by all examiners on questions and answers and more notes are made of the examiners' opinions of the candidate's responses. Regardless of whether he and his judges agree or disagree over controversial questions, his logic and his defense of his viewpoint are the essential points considered.

That same evening, while the details are still fresh in everyone's mind, the Board and Associate Examiners meet to review the day's work. Each candidate's showing is discussed individually. Over those not passing or questioned by their examiners, a detailed and sometimes prolonged discussion takes place. Questions and answers are reported to the entire group of eighteen by the first examiners, followed by a similar detailed report with recommendations from the referees, and another from the laboratory examiners. Warm disagreements and arguments often take place and the entire group enters into these, final action in such cases as in all others being taken by an open vote of the entire Board. It would be utterly impossible for any bias or personal prejudice to creep in; it would be equally impossible for any one or two examiners to reject a candidate because they must report in detail to the entire Board with all of the Associate Examiners, and any dissenting opinion between two or more sets of examiners must be justified; the laboratory examiners must agree, and before any candidate can be failed the entire Board must be convinced that this action is proper, final action being taken by an open vote. Thus, it is much more difficult to fail than to pass a man before this Board, strange as that may seem.

Critics of this Board and of the other American Boards, and, in fact, of the whole subject of certification of specialists, have been loud and bitter. The Boards have been accused of discriminating against lesser trained specialists, usually self-styled as such, against young medical men struggling to establish themselves, and against general practitioners, though how this last is done is not entirely clear. They have been accused of setting up a political bloc, although all of the Boards have attended strictly to their business as examining and certifying bodies.

They have been accused of attempting to establish a medical aristocracy, and if, by certifying, on the sole basis of proved proficiency, men and women of all colors and all races and all religions practicing as specialists in this country, an "aristocracy" is made, then this charge is true. Under this "aristocracy," however, the sick public is protected as it was not protected fifteen or twenty years ago.

We have seen results in respect to that first of our original stated purposes, namely, to elevate the standards and advance the cause of obstetrics and gynecology.

During our earlier years, the predominance of failures occurred in the laboratory branches of the examinations because this aspect of obstetrics-gynecology had been neglected in training, with emphasis concentrated on clinical activities. That situation has entirely changed, the majority of men coming before us now having made a distinct effort to perfect themselves in gross and histo-pathology, and other basic science subjects of the specialty.

Our requirements for training, in order to make better specialists whom we could certify, created a demand for facilities where such training could be acquired. In 1930, when this Board began to function, there were 167 residencies in either or both branches of our specialty approved for training by the Council on Medical Education and Hospitals of the A. M. A. This latter group has performed remarkable service to the public in its surveys and regulations

judicial, unbiased standards, and that medical politics, local jealousies, or prejudiced views never be allowed to exert any influence.

Any responsible authority in obstetrics and gynecology who may think he has reason to doubt the absolutely unswerving fairness of our examinations and other proceedings is quite likely to find himself invited, if he is of professorial rank, as our examiners must be, to sit with the Board as an Associate Examiner at its next examination. He will come away as have others in the past, entirely convinced that an unfair or uneconsidered action against a candidate is impossible, and he is likely to be among the Board's staunchest supporters from that time on. The sole exception to this in our fifteen years' experience was one Associate Examiner who was himself unusually severe in his judgment of candidates, but who protested and still does so over the failure, a year or two later, of a man in whom he happened to be personally interested. The others who have participated from time to time will not allow a charge of unfairness or bias to remain for an instant unchallenged.

All of you are familiar with our methods of investigating the background of special training, ethical standing in the community, and professional recognition of ability of all candidates. It is not necessary, therefore, to elaborate on this subject.

You may know of some men who have been admitted to examinations and have been certified, but who, in your opinion, should not have been. You may be right about this, but we could not have had sufficient positive information to warrant nonacceptance of these men as candidates. According to their verified records they met our requirements, and they proved able to pass the examinations. We depend heavily upon our diplomates to stand guard for us in their communities, but we must have specific information if we are to rule against a man. Furthermore, we have never violated any confidential communication. What are obviously isolated, local jealousies are disregarded, and anonymous letters or unsigned complaints against candidates or diplomates are consigned to the wastebasket.

We have to depend also on our diplomates to stand guard against infractions of regulations of specialty practice on the part of those holding certificates. We have not hesitated to withdraw a small number of certificates, and an additional few have been surrendered voluntarily.

What you may be less familiar with are some of the things that go on behind the scenes at the times of examinations.

The written examinations are compiled by an Examination Committee from sets of questions submitted by each of us on the Board. Papers and case records from any community are rigidly assigned for review and gradings to examiners in communities distant from that of the candidate. No examiner will ever participate in the judging of a candidate with whom he is personally acquainted.

At the time of the oral examinations, a candidate meets one or more teams, each consisting of a Director of the Board and an invited associate examiner, for his oral examination, and he goes also to two additional examiners for an examination in gross and microscopic pathology.

The candidate is given every possible opportunity to acquit himself favorably, as we greatly prefer to pass men rather than to fail them, and it must always be remembered that each one of these candidates has had training satisfying the Board's rigid requirements before ever being admitted to the examination.

If the first team of oral examiners has any doubt about a candidate, even to the extent of thinking that they have upset his poise and strained his "nerves," they send him to referee examiners rather than to take final adverse action. To

11 have been withdrawn or surrendered, 129 cancelled by death, 2,044 still remaining in effect.

The public has been served both in time of peace and in time of war by the lists of certificate holders.

Moreover, we of the Boards and many of you holding certificates believe that the entire medical profession has been benefited and standards of practice generally improved by this movement for certification of specialists. The Boards have never had any desire to interfere with or limit the professional activities of any licensed physician. Their chief aim has been to standardize and improve general qualifications for specialization, and by certification to make available the names of those who are qualified and not merely "self-styled" specialists, as in former days. As stated before, in the establishment of more and better training facilities which a few use to the limit, all of the profession have acquired vastly increased opportunities for improving themselves to whatever extent they wish.

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governing hospital practice. Its approval of residency training facilities has been the criterion under which the Boards, in general, have acted on the subject of what constitutes satisfactory or acceptable training in the specialties.

By 1935, the number of approved residency positions available in our specialty had increased from 167 to 245; in 1940 these numbered 269; and in 1945 reached the mark of 656. In 1946 there were 768.

Can there be any doubt that under the rigid and intensive educational standards that must be maintained by a hospital to retain its approval listing, all of its young physicians are much better trained under skillful supervision to meet the emergencies of obstetric and gynecologic practice than by the old method of "sink or swim"? Yet only recently the editor of a State Medical Society Journal wrote in criticism of American Board certification and requirements for these as follows: "Before this tragedy (of "impossible" requirements) occurred, we were all agreed that five or ten years of rural practice were the finest kind of training for any career in medicine."

Well, were we all agreed, and what would some of the families of dead mothers and babies say on this subject? Be that as it may, it is a fact that coincident with the establishment of these training requirements and the fifteen years of certification, the maternal death rate in this country fell more rapidly than in any other similar period, due *partly*, I maintain, to the fact of better teaching of obstetrics and gynecology and better training in practice of this specialty. Do not forget that it is by no means solely these interns and residents who go on to certification from these training centers that benefit from the bettered teaching standards, but also all who serve in them.

The general standards of practice of obstetrics and gynecology cannot help improving in these hospitals where residency teaching is being done, a statement that does not need to be elaborated. In the end it is the patient who benefits.

The medical public, including that important section of the profession, the general practitioner, can and has also benefited the lay public by being better able to determine who are recognized, according to fixed standards, as qualified specialists in all branches in all parts of this country and in Canada. The Directory of Medical Specialists publishes lists of all specialists certified by American Boards, and these are widely circulated.

When the Army and Navy mobilized vast numbers of men and women for military service, they desired as a primary function of their medical departments that that personnel be given the best possible medical care. It is quite true that as a general thing, and so far as possible, Diplomates of American Boards were given military assignments appropriate to their training. Specialists were needed for special work, and the Services quite naturally used American Board certification as a criterion of what constituted a specialist. Moreover, the Boards had seen to it that these men had been better trained in their specialties than were similar groups in World War I. Could not some of this have contributed to the fact that only about 2 per cent of our wounded personnel in World War II died of complications following their wounds as compared with approximately 11 per cent in World War I?

Thus it appears that, like the others, our Board in its fifteen years of existence has succeeded to some extent in carrying out its proclaimed purposes.

The standards of the practice of our specialty have been elevated; the Board has fairly determined to the best of its ability, the competence of those voluntarily appearing before it and professing to be specialists in obstetrics and gynecology; its examinations of candidates, though growing steadily more and more rigid, have always been impartial and judicial in their conduct and control; 2,184 certificates of qualification as specialists have been issued, of which

of convulsive seizures. In summarizing their work, the authors state that nerve tissue is more sensitive to oxygen deprivation than any other types of body tissue. This tends to be most marked at the highest neurologic levels. It is further believed that fetal and neonatal anoxia in humans may play a major part in the development of epilepsy.

HARVEY B. MATTHEWS

Peralta Ramos, A.: Identification of the Newborn, *Obst. y ginec. latino-am.* 3: 839-847, 1945.

From the social viewpoint, the identification of the newborn is transcendental, the dactyloscopic system being the only one giving full security. Vucetich, in 1891, was the first who studied and classified fingerprints, thus establishing a simple, rapid, and safe method for the identification of any person.

At the Maternity Institute of which the author is the chief, and where the birth rate is as high as 7,000 deliveries every year, this system has been introduced and successfully solved long ago, thanks to the establishment of a specialized staff (five nurses in this case), that not only realizes the mechanical part of the task (the taking of the prints), but also the identification of the individual through the interpretation of these prints.

It is not only in hospitals that such impressions should be taken, but also in homes.

The impression taken at birth must be included in the school as well as in the military and labor documents, for the reason that if the name is modified, concealed, or substituted by another person, this cannot occur with the dactyloscopic impression.

J. P. GREENHILL

Martinez, Carmona Elisardo: Study of the Etiological Factors of Prematurity, *Rev. espñ. de obst. y ginec.* 4: 285-293, 1946.

The authors studied the causes of prematurity which occurred at the Barcelona Maternity for 1923 to 1944. The frequency of prematurity in this institution was 9.37 per cent.

The chief causes of prematurity from 1923 to 1926 at the Barcelona Maternity were as follows:

Twins	15.8 per cent
Syphilis	14.2 per cent
Toxemia	12.4 per cent
Premature rupture of the membranes	8.9 per cent
Placenta previa	3.0 per cent
Tuberculosis	1.8 per cent
Unknown	32.0 per cent

From 1937 to 1944 the most important causes of prematurity were as follows:

Syphilis	16.5 per cent
Twins	10.0 per cent
Premature rupture of the membranes	9.8 per cent
Toxemia	7.4 per cent
Placenta previa	3.2 per cent
Tuberculosis	1.7 per cent
Unknown	43.2 per cent

J. P. GREENHILL

Gesteira, Martagao: The Care of Premature and Congenitally Weak Babies, *An. brasil. de ginec.* 21: 281-295, 1946.

This paper deals with the care of premature and congenitally weak babies. The author condemns the daily cleansing bath during the first few days of life. He advocates a hot bath beginning at 26° C., and gradually increasing to 40° C. which may be given once as a treatment to raise the temperature of a weak baby. He advocates the use of oxygen in incubators as well as oxygen tents or by means of an insufflation apparatus. He discusses the importance of syphilis and erythroblastosis as etiologic factors both in prematurity and congenitally defective babies. Vitamins and hormones are recommended to increase the resistance of small babies.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Newborn

Kariher, Donald H., and Miller, Dorothy I.: Evidence of Maternal Rh Sensitization Without Evidence of Hemolytic Disease in the Newborn, *Am. J. M. Sc.* 212: 327, 1946.

Two interesting cases are reported by Kariher and Miller in which normal infants were born to Rh-negative mothers whose blood showed a relatively high concentration of Rh antibodies. In the first case, this was the mother's second pregnancy, the first having been interrupted at two months by a criminal abortion. Thus it is questionable whether the mother had never received a blood transfusion.

The second case was that of a baby born to a mother who had had two children, both perfectly normal. The third baby was carefully observed for evidence of hemolytic disease, both from the clinical and laboratory points of view, but none was noted.

The authors state that theirs is only the third report in the literature of cases of this kind. They offer two theories, both equally plausible, which might explain this apparently rare occurrence. Finally, in spite of the satisfactory outcome in these two cases, the obstetrician and pediatrician are urged to exercise every precaution in cases of pregnant women who are Rh negative and in whose serum are found Rh antibodies.

HERBERT J. SIMON.

Falls, Harold F., and Jurow, Harry N.: Effect of Antepartum Vitamin K on Retinal Hemorrhage, *J. A. M. A.* 131: 203, 1946.

The fundi of 432 consecutive infants were examined at the Maternity clinic of the University of Michigan Hospital twenty-four to forty-eight hours after birth. Eighty-three of the 432 cases were followed by determining the prothrombin time of the infants seventy-two hours after birth, and again at nine days after birth. There is a difference of 1.3 per cent in the two groups checked—one group having received vitamin K ante partum, and the other group not. There was a significant elevation (about 10 per cent) in the seventy-two-hour prothrombin level in infants whose mothers received vitamin K. The authors feel that hypoprothrombinemia cannot be conceived as effecting an endothelial change. Actual trauma and anoxia seem to be the more important factors in the production of hemorrhages in the retina of the newborn. The authors conclude that vitamin K, either antepartum or intrapartum, does not reduce the incidence of retinal hemorrhages in the newborn.

WILLIAM BERMAN.

Fender, Frederick A., Neff, William B., and Binger, Grace: Convulsions Produced by Fetal Anoxia; An Experimental Study, *Anesthesiology* 7: 10, 1946.

The authors were interested in the possible relationship between anoxia and the convulsive states in the human, and set up a series of experiments on dogs in an effort to show that anoxia in the unborn fetus or newly born young can lead to convulsive states later in life. The central nervous system demands a great amount of oxygen for normal function. This fact has been known for many years, but not until recently has any recognition been accorded the role of anoxia in the unborn fetus or the newly born child to future development.

**Agliero, Oscar:** The Weight of Normal Pregnant Women, *Rev. de obst. y ginec.* 6: 95-101, 1946.

The author studied the weights of 432 pregnant women seen at the Concepcion Palacios Maternidad in Caracas. He found that the average gain in weight was 9 Kg. (19.8 lbs.). In 53 per cent of the patients, the greatest gain was in the third trimester of pregnancy. Multiparas showed a greater tendency to gain weight than primiparas. Multiparas gained on an average of 9.57 Kg. (21.1 lbs.), whereas primiparas gained on an average of 8.64 Kg. (19 lbs.). The age of the mother had no influence on the amount of weight gained. Neither the duration of labor nor the frequency of operative intervention had any relationship to the amount of gain in weight. On the other hand, the weight of the baby increased in direct relationship with the maternal gain in weight.

J. P. GREENHILL.

**Murray, Blair E.:** Some Observations on the Role of Protein in Pregnancy, *West. J. Surg.* 54: 288, 1946.

The obstetrician should be interested in protein metabolism from two standpoints: (1) obstetrical shock, and (2) obstetrical diet. Protein is a colloid substance of large molecule, relatively impermeable to tissue membrane, and, therefore, of the greatest importance in maintaining water equilibrium between the vascular system and the intercellular spaces. Loss of protein from the vascular system in shock or hemorrhage is most conveniently replaced by the use of human plasma. Animal plasma has been broken down into five protein fractions. The most important of these, albumin, has been isolated in pure form and may be used as a quick acting and powerful means of increasing the osmotic pressure in the vascular system. The author stresses the point that amino acid solution must not be confused with these new protein solutions; the amino acids have value as food, but do nothing to combat shock.

The importance of protein in the obstetric diet is emphasized. Edema may be prevented and the incidence of toxemias reduced by high protein, low salt diet. Skim milk powder is a practical means of giving protein.

WILLIAM BICKERS.

### Pregnancy, Complications, Toxemia

**Neary, Edward R.:** The Use of Molybdenized Ferrous Sulfate in the Treatment of True Iron Deficiency Anemia of Pregnancy, *Am. J. M. Sc.* 212: 76, 1946.

The hydremia that is almost always associated with pregnancy results in an apparent anemia. However, many women do have a true hypochromic anemia during pregnancy. A group of these cases was treated by Neary with molybdenized ferrous sulfate, and another group with plain ferrous sulfate. The results of this carefully controlled work indicated that patients treated with the molybdenized iron showed a therapeutic response which was sustained until normal hemoglobin levels were obtained. In contrast, those patients treated with simple ferrous sulfate showed an initial favorable response and then apparently reached a plateau at which the hemoglobin levels were still subnormal. This persisted in spite of continued treatment. When the molybdenized product was given to these patients, their hemoglobin values again rose until a normal figure was reached. From this work it would appear that molybdenized ferrous sulfate is more effective than plain ferrous sulfate in the treatment of iron-deficiency anemia of pregnancy.

HERBERT J. SIMON.

**Watson, Janet, and Castle, William B.:** Nutritional Macrocytic Anemia, Especially in Pregnancy, Response to a Substance in Liver Other Than That Effective in Pernicious Anemia, *Am. J. M. Sc.* 211: 513, 1946.

In this article Watson and Castle discuss the causes of the failure of response in certain cases of nutritional macrocytic anemia, especially in pregnancy, to purified liver extract. It would appear that the unitarian concept, suggested earlier by Strauss and

The author also emphasizes precautions against infection. He points out the advantages of human milk, but maintains that this ideal food does not entirely meet the requirements of premature babies. He uses supplemental, synthetic substances, salts, and proteins. For many years he has followed Hess' schedule of feeding as used at the Sarah Morris Premature Infant Station.

J. P. GREENHILL.

## Placenta

Solomons, Edward, and Falkiner, Ninian McL.: Calcification of the Placenta, Irish J. M. Sc. 243: 99, 1946.

The authors present a short review of the current literature on calcification of the placenta. In addition, they present an instance of two successive pregnancies in the same patient where marked calcification was present in both placentas. In the first pregnancy the mother fell into labor normally at term and was delivered by outlet low forceps of a stillborn infant. No cause for the stillbirth could be determined, but there was marked calcification of the maternal plate of the placenta and of the villous tree, especially around the periphery. The authors felt that the extensive calcification of the placenta might have been responsible for the fetal exitus, and therefore in the mother's next pregnancy a cesarean section was performed in the thirty-eighth week. This time a living baby was obtained, and the placenta showed pathologic changes similar to the first placenta. In both pregnancies the blood chemistry in regard to serum calcium, acid and alkaline phosphatase, and plasma phosphates was normal. There are three microphotographs of these placentas and two gross photographs showing the location of the calcification.

L. M. HELLMAN.

## Pregnancy, Physiology

Shute, Wallace, and Shute, Evan: The Prevention of Premature Labor, J. Obst. & Gynaec. Brit. Emp. 52: 570, 1945.

In 63 cases of threatened or actual premature labor, 20 of the patients gave a history of previous abortions or "other abnormal terminations" of pregnancy. These patients were treated with vitamin E, and 46 living infants were delivered, a salvage of 73 per cent. In the patients in this group who had a blood estrogen determination made, 87 per cent showed a high estrogen level early in pregnancy. Combining the results reported in this series with a previous series in which vitamin E was used in the treatment of threatened premature labor, there were 92 normal living children born to 109 patients. In the entire series there were only six malformed children, only one of which (with a cleft palate) lived more than three months. If vitamin E is used in the treatment of threatened abortion or premature labor, a product of proved potency must be employed in adequate dosage. Dosage must be determined in each case, depending upon the severity of the symptoms and their duration. Treatment must be continued until term. The authors are of the opinion that routine determinations of blood estrogen should be done on pregnant women when they first report for antenatal care. In this way prophylactic treatment with vitamin E can be given when indicated by a high blood estrogen level. The patient is instructed to report if any slight abnormal symptom develops, such as an area of uterine tenderness, sacral backache, or spotting of blood, when the dosage of vitamin E can be increased.

HARVEY B. MATTHEWS.

von Wattenwyl: The Frog Test of Pregnancy, Gynaecologia 121: 29-46, 1946.

The author reports 182 pregnancy tests using clawed toads (Hogben's test); according to the results obtained there were only 3 per cent incontestable erroneous results. A positive reaction is considered a reliable sign of an undisturbed pregnancy. In comparison with the Aschheim-Zondek reaction, the simpler technique of the frog test and the short reaction time required for the test are an improvement.

J. P. GREENHILL.

Andrew, Wilson, and Barr, S. James: *Myasthenia Gravis and Pregnancy*, J. Obst. & Gynaec. Brit. Emp. 52: 584, 1945.

In the case reported, the patient had had myasthenia gravis for eighteen months; symptoms were satisfactorily controlled by prostigmin (15 mg. three times a day) and ephedrine ( $\frac{1}{2}$  grain twice a day). When she became pregnant there was no change in her condition until the beginning of the second trimester, when a slight increase in the amount of prostigmin was necessary (60 mg. daily). Labor was normal and delivery was spontaneous; there was no evidence of any exhaustion of the voluntary musculature, and no signs of any inortia or fatiguo of the uterus. There was a transient mild relapse of the myasthenia gravis, necessitating another slight increase in the dosage of prostigmin, which occurred during the first five days after labor. By the fifth day, the patient's condition was the same as in the last half of pregnancy; and on the ninth day a definite remission of the myasthenia gravis began which continued for nine months, so that symptoms were controlled by a smaller dose of prostigmin than was required before pregnancy; the patient nursed the child for seven months of this period. After this nine months' remission, the dosage was raised to the pre-pregnancy level for adequate maintenance. The child was normal at birth and has developed normally. This case and a review of the literature led the author to conclude that there is no indication that pregnancy, labor, or nursing affects the course of myasthenia gravis adversely, if the patient is adequately treated with prostigmin and ephedrine.

HARVEY B. MATTHEWS.

Barnes, Josephine, and Browne, F. J.: *Blood Pressure of Patients With Toxemia of Late Pregnancy*, J. Obst. & Gynaec. Brit. Emp. 52: 559, 1945.

It is well known that a tendency to high blood pressure and the diseases associated with it may affect members of the same family, and this tendency is generally supposed to be hereditary, although this conclusion is based on studies of individual families rather than on a statistical survey. Many cases have been reported of eclampsia occurring in members of the same family; and a tendency to hypertension has been noted in families of patients who have developed eclampsia or late toxemia of pregnancy.

Blood pressure was recorded in 226 relatives of 129 patients admitted to the hospital with late toxemia of pregnancy, and in 66 relatives of 47 patients admitted toward the end of pregnancy without toxemia. There was no essential difference in the levels of the blood pressure in the relatives of the toxemic and nontoxemic pregnant patients, except in the group of toxemias classified as essential hypertension of pregnancy. In this group the incidence of hypertension in the family was higher than in other types of toxemic or in nontoxemic patients. Of 18 mothers of the patients with essential hypertension of pregnancy whose blood pressure was recorded, 16 showed marked hypertension. On the basis of these findings the authors conclude that it is rarely necessary to interrupt pregnancy in patients with essential hypertension unless the hypertension is of the malignant type. Patients with malignant hypertension should be advised not to become pregnant. Patients with a familial history of hypertension should not be discouraged from having children, except in those cases in which the manifestations of hypertension have occurred often and at an early age.

HARVEY B. MATTHEWS.

Bonilla, F., and Paisan, J.: *Anemia and Pregnancy—Hematology*, Rev. españ. de obst. y ginec. 4: 213-229, 1946.

The authors made a study of the blood of 682 pregnant women. They found that the average results were as follows:

Erythrocytes 44,000,000  
Hemoglobin 14.4 grams  
Hematocrit volume 42 per cent  
Corpuscular volume, 91 cubic micra  
Volumetric Index 1.04  
Corpuscular hemoglobin 28 to 34 milligrams

Castle, does not apply to the cases herein reported. Further, these cases failed to show many of the clinical and laboratory criteria necessary for the diagnosis of true Addisonian anemia. In this communication the authors suggest that there may be another factor present in the various liver extracts and in autolyzed yeast. They initiate the term "Wills' factor" for this, as yet, hypothetical substance.

Four cases, two of which occurred during pregnancy, are reported that failed to respond to different types of liver extract administered parenterally in the usual doses. Three of the cases showed an immediate and striking response to two types of liver extract when given by mouth. The fourth case responded very well when the dose of the parenteral liver extract was increased tenfold. In one case, in order to prove that Wills' factor was not identical to any of the several pure components of the vitamin B complex or with "Folic Acid," they were administered in large doses without producing any response. It is of importance to the obstetrician to remember that a rare case of nutritional macrocytic anemia in pregnancy which fails to respond to the purified liver extracts may react to relatively crude oral liver extracts. Finally the authors emphasize the demonstrated therapeutic values of the parenterally administered refined liver extract in the vast majority of cases of nutritional macrocytic anemia.

HERBERT J. SIMON.

Thomas, Rufus C.: Rupture of the Rectus Abdominis Muscle During Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* 52: 580, 1945.

The author has previously reported a case of rupture of the rectus abdominis muscle during pregnancy, and reports a second case in this article. In this case the patient had had five previous normal pregnancies and deliveries and one abortion. She was admitted to the hospital when about thirty-three weeks pregnant, with a history of bronchitis and pain in the abdomen when she coughed; a "lump" had also been noticed in the region of the right rectus muscle. While a diagnosis of concealed accidental hemorrhage was made, the uterus was softer than it would be with such a hemorrhage, that produced abdominal tenderness. While under observation she developed typical symptoms of internal hemorrhage, and operation was done. This showed a tear in the right rectus muscle with bleeding from a branch of the deep epigastric artery and another smaller vessel; blood clots were removed, the bleeding arteries ligatured, and a pack placed along the deep surface of the rectus muscle, and brought out through the lower end of the incision, which was then closed. On the fifth day after operation, the patient was delivered of a stillborn child. The patient finally made a good recovery, which was delayed by a reaction to an incompatible blood transfusion. A review of the literature shows this to be the thirty-second case reported of rupture of the rectus muscle during pregnancy; the correct diagnosis was made before operation in only nine of the 32 cases. Cullen's sign was present in five of the cases, including the case reported. The maternal mortality was 13 per cent, the fetal mortality about 50 per cent. Conservative treatment is justified in these cases only if the patient's condition remains good; if signs of increasing hemorrhage and shock develop operation is indicated.

HARVEY B. MATTHEWS.

Wespi, H. J.: Transfusion Death of a Woman Recently Delivered of a Hydrops Fetus and Placenta. The Clinical Significance of the Rh Factor, *Gynaecologia* 121: 47-57, 1946.

The author gives a description of a fatal case due to transfusion in a para vi patient on whom embryotomy had to be performed because of obstruction in labor caused by hydrops of the fetus and placenta. Ten minutes after transfusion of 400 c.c. of citrated blood of the same group cyanosis and dyspnea, and four hours later death occurred. The previous history was important; after two normal deliveries, there was icterus gravis of the third child and stillbirths in the fourth and fifth pregnancies, therefore the typical picture of hereditary erythroblastosis. The author discusses recent investigations of the Rhesus factors and their importance for the origin of erythroblastosis and accidents in transfusion. The present case corresponds in a classical way with the results of these investigations. The author also takes up the matter of prevention of accidents in transfusion, especially by avoiding transfusions in women who had given birth to dead children.

J. P. GREENHILL.

was observed in 85.1 per cent of the cases, whereas when both the ovaries and the pituitary gland were irradiated the incidence of success was only 42.8 per cent. In the opinion of the authors, this is evidence that the ovaries are primarily at fault.

J. P. GREENHILL.

**Lobo, Joao Bruno:** Antiphlogistic Roentgen Therapy of Adnexal Disease, *An. Brasil. de Ginec.* 21: 350-367, 1946.

The author reviews the literature of roentgen therapy for adnexal inflammation, and also discusses the results of a series of 47 personal cases. In 83 per cent of 18 cases where complete blood studies were made, favorable results were observed. In one case treatment of right adnexal inflammation was followed by inflammation on the opposite side, and in two other cases there was no favorable response.

The author believes that the roentgen therapy has no adverse effect on offspring with the doses he uses.

J. P. GREENHILL.

### Sterility, Contraception

**Kamman, Gordon R.:** The Psychosomatic Aspects of Sterility, *J. A. M. A.* 130: 1215, 1946.

The author reviews the psychosomatic concept of sterility and fertility. The literature is reviewed with reference to the nervous influence on ovulation. It is felt that the neuro-endocrino control of ovulation probably has its center in the pituitary gland, and this gland is in direct neural connection with the thalamus and hypothalamic centers which are intimately concerned with emotional life of man. It is theoretically possible that emotional stimuli either are accompanied by, or result in inhibition of pituitary function.

WILLIAM BERMAN.

**Guerrero, Carlos D.:** Sterility; A Study of Its Investigation and Treatment, *Obst. y ginec. latino-am.* 4: 208-230, 1946.

The author reports a study of 438 cases of sterility. Of these, 65 per cent were primary sterility cases, and 35 per cent were secondary. The husband was responsible in 29.2 per cent of the cases. Tubal factors were involved in 31 per cent, hormonal factors in 16 per cent, cervical factors in 11 per cent, and retroflexion of the uterus in 2.8 per cent. In 10 per cent of the cases there was no follow-up study.

Among the 438 patients, 44 became pregnant, or approximately 10 per cent. Of these 44 pregnancies, 26 went to term, five had premature deliveries, eight had abortions, one had an extrauterine pregnancy, and four are still pregnant. The following tests were performed on these 438 patients:

The Rubin kymographic test	437
Hysterography	152
Endometrial biopsy	163
Various hormonal medications	23
Vaginal treatment	64
The Huhner test	28
Sperm studies	76
Surgical intervention	31

The surgical interventions were as follows:

Salpingostomy	18
Implantation of the tube	4
Myomectomy	7
Estes operation	2

The author concludes that the ideal treatment of sterility is not surgical.

J. P. GREENHILL.



The incidence of anemia in this series was 12.4 per cent.  
The various types of anemia were divided as follows:

I. Macrocytic type	
(a) Hyperchromic	3.5 per cent
(b) Orthochromic	53.0 per cent
(c) Hypochromic	17.7 per cent
II. Normocytic type	
(a) Orthochromic	15.2 per cent
(b) Hypochromic	5.9 per cent
III. Microcytic type	5.0 per cent

J. P. GREENHILL.

Moscoso, César Jacome: Large Ovarian Cysts With Torsion of the Pedicle During Pregnancy, *Obst. y ginec. latino-am.* 4: 96-106, 1946.

According to the author, statistics reveal that the operative mortality for the removal of ovarian cysts during pregnancy is low, varying from 0.3 per cent to 0.47 per cent. On the other hand, the mortality rate for similar operations during the puerperium is very much higher, namely 10 per cent.

He reports two cases of pregnancy associated with cystadenoma of the ovary in which there was torsion of the pedicle during pregnancy. The author emphasizes that ovarian cysts seldom influence the course of pregnancy. Likewise, pregnancy is usually not interrupted by torsion nor by operation for the removal of the cyst. In most cases gestation continues to term, labor is normal, and the babies are normal.

J. P. GREENHILL.

## Menstruation

Martini, Juan Livio: The Vaginal Cycle in Amenorrhea Associated With Lactation, *Obst. y ginec. latino-am.* 4: 273-280, 1946.

The author studied the changes in the vaginal mucosa of five women who had amenorrhea during lactation. All were young primiparas between 20 and 25 years of age without any antecedent pathology and without any systemic ailments. The length of the amenorrhea varied from three to eight months when the studies were undertaken. The duration of the studies were from thirty-eight to sixty days. In four of the five cases the vaginal mucosa was in a condition of repose or mild atrophy which corresponded to an ovarian insufficiency of moderate intensity. This limited study does not permit definite conclusions, but it does appear that a certain degree of insufficiency exists in the ovarian function in the amenorrhea of lactation.

J. P. GREENHILL.

## Roentgen Rays

Guitarte, Arturo: Roentgen Stimulation of the Ovaries, *An. brasil. de ginec.* 21: 191-201, 1946.

This paper concerns the use of roentgen-ray therapy for the purpose of stimulating the ovaries when hormone therapy has failed. The author reviews the literature on this subject and maintains that only cases of primary functional disturbance of ovarian origin will be benefited by roentgen ray therapy. He also refers to the stimulating effect of roentgen therapy to the anterior pituitary lobe, and describes the technique involved.

In order to avoid harm to the offspring, the author insists that contraception should be practiced for six months following treatment. Furthermore, roentgen-ray therapy to the ovaries should be carried out only in a few select clinics.

J. P. GREENHILL.

Salaber, J. A., Molinari, J. L., and Sardi, J. L.: Stimulative Roentgen Therapy in the Treatment of Ovarian Insufficiency, *Obst. y ginec. latino-am.* 3: 1-9, 1945.

The authors report a series of 34 women treated with roentgen-ray therapy because of disturbances of the genitals. In the women who had irradiation of the ovaries alone, success

## Necrology

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JAMES EDWARD KING, M.D., gynecologist, of Buffalo, New York, died there March 10, 1947, at the age of 73 years. Dr. King graduated from the University of Buffalo School of Medicine in 1896, became Professor of Gynecology in his Alma Mater, later Emeritus, was attending gynecologist in the Buffalo General Hospital, and consultant to several others. He was a Fellow of the American College of Surgeons, the American Gynecological Society, the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, President of the latter in 1938-1939.

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## Items

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### American Board of Obstetrics and Gynecology, Inc.

#### Examinations

The next oral examination and annual meeting of the American Board of Obstetrics and Gynecology, Inc., will be held at the Hotel William Penn, Pittsburgh, Pa., June 1 to 7, inclusive.

The following associate examiners have been appointed to assist the Directors of the Board: Dr. W. C. Danforth, 636 Church St., Evanston, Ill.; Dr. John L. Parks, Gallinger Municipal Hospital, Washington, D. C.; Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland, Ohio; Dr. S. A. Cosgrove, 88 Clifton Place, Jersey City, N. J.; Dr. L. M. Randall, Mayo Clinic, Rochester, Minn.; Dr. Nicholson J. Eastman, Johns Hopkins Hospital, Baltimore, Md.; Dr. Conrad G. Collins, Tulane University, 1430 Tulane Ave., New Orleans, La.; Dr. William J. Dieckmann, 5841 Maryland Ave., Chicago, Ill.; Dr. C. B. Lull, 807 Spruce St., Philadelphia, Pa.; Dr. J. R. Eisaman, 121 University Place, Pittsburgh, Pa.; Dr. Herbert E. Schmitz, 25 E. Washington St., Chicago, Ill.

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The following physicians are to be included in the list of diplomates certified by the American Board of Obstetrics and Gynecology: Dr. Henry Woodward Clapp, 320 Lyman Bldg., Muskegon, Mich.; Dr. Frederick Sheer, 2702 Avenue S, Brooklyn, N. Y.

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## Erratum

A regrettable error occurred by including the paper by Dr. Leon C. Chesley et al., entitled, "Pregnancy in the Patient With Hypertensive Disease," with the *Transactions* of the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, which were published in the March issue of the JOURNAL. The Prize Essay will appear in a subsequent early issue.

## Venereal Diseases

Ingraham, Norman R., Stokes, John H., Beerman, Herman, Lentz, J. W., and Wammack, Virgene S.: Penicillin Treatment of the Syphilitic Pregnant Women, *J. A. M. A.* 130: 683, 1946.

The authors report the treatment of 49 pregnant women (40 Negro and 9 white) with penicillin. In this group only one syphilitic infant occurred among 37 syphilitic pregnancies treated with penicillin, which reached term. Either 1.2 million or 2.4 million Oxford units is satisfactory, although the authors prefer the larger dose. It is recommended that the dosage be reduced to one-fourth during the first twenty-four hours, and to one-half during the second twenty-four hours to reduce the possibility of threatened abortion from therapeutic shock, and the duration of treatment be prolonged to eight or nine days. The serologic response to penicillin treatment of the pregnant woman is apparently considerably slower than the average for early acquired syphilis in the adult. It is not necessary for the mother to be seronegative at the time of confinement in order for the infant to be normal.

The average length of time after penicillin until sustained seronegativity was obtained in 20 cases which have become seronegative was 190 days. The most rapid case reverted to seronegativity on the twenty-second day. The longest case to become seronegative occurred on the three hundred and sixty-fifth day.

WILLIAM BERMAN.

## Malignancies

Covington, Eugene E.: Cancer of the Cervix. A New Technique for Interstitial Implantation of Radium into the Parametrium, *Surg., Gynec. & Obst.* 82: 512, 1946.

The author describes a new technique for radiation therapy in carcinoma of the cervix. This technique enabled him to administer a greater dosage of radium without ensuing complications. During the first treatment 3,600 mg. hours of radium with a 1 mm. platinum filter is used in more or less a routine manner, care being taken not to bunch the radium over the cervix, but to distribute the tandems as far laterally into the vaginal fornices as possible. Within a few days of the first treatment 2,000 to 2,400 roentgen units were given to each of four pelvic fields over a period of four weeks. As soon as the roentgen therapy was completed, a second interstitial implantation of radium was done by making four small incisions into the vaginal mucosa at equally distant points as far lateral from the cervix as possible. These incisions were carried down through the mucosa only, and then a long Kelly clamp was used to dissect a tract into the parametrium. Four rubber tandems made up as follows: two tandems of 25 mg., two tandems of 20 mg.; two tubes of 10 mg. were then used in the following manner. A rubber tandem was then inserted into each of the four tracts and a long rubber tandem was inserted into the vaginal canal. Five grams of sulfanilamide were applied locally, and the vagina was packed with gauze. By this method a total dosage of 7,800 mg. hr. of radium, plus 3,360 roentgen units were given. There were no early complications, but six of 100 cases so treated developed irradiation proctitis. There was one instance of a rectovaginal fistula, and one of radiation necrosis of the cervix. Although this is not a five-year study, there have already been 24 deaths as a result of uncontrolled cancer of the adjacent parametrium. Seventy-six patients are still alive

L. M. HELLMAN.

- St. Louis Gynecological Society. (1924) *President*, Otto Krebs. *Secretary*, John E. Holibs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society. (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists. (1930) *President*, T. F. Bunkley. *Secretary*, J. Melver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists. (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists. *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society. *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society. (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stinson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society. (1912) *Secretary*, Emmett A. Meehler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology. (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society. (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology. (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society. (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society. (1944) *President*, Wynne M. Silbernagel. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttes Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society. (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society. (1924) *President*, George Museillo. *Secretary*, Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society. (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society. (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society. (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society. (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada. (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society. (1946) *President*, L. L. Bottsford. *Secretary-Treasurer*, N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology. *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society. (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society. (1947) *President*, M. E. Grier. *Secretary*, B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Norris Vaux, Philadelphia, Pa. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Alice F. Maxwell, San Francisco, Calif. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas, Tex. Annual meeting Atlantic City, June, 1947.
- New York Obstetrical Society.** (1863) *President*, Harvey B. Matthews. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, F. Sidney Dunn. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Ralph A. Reis. *Secretary*, Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Samuel S. Gordon. *Secretary*, J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Charles J. Barone. *Secretary*, Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Frederick J. Lynch. *Secretary*, Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Goodrich C. Schaffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, Lawrence Lee Cokerille. *Secretary*, Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Eugene H. Countess. *Secretary*, Joseph W. Reddock, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

ism was of the "rugged" variety. It is fortunate for us that this was so. They founded an association for the encouragement and promotion of the study and practice of obstetrics and gynecology, and they based their hopes for its success on the individual enthusiasm of the younger generations of obstetricians and gynecologists who would comprise its membership. At the same time, they recognized that enthusiasm needed experience to guide it. They supplied that experience in many ways during the early years of this Association's life, but, always, with the emphasis upon the individual. From the combination of enthusiasm and experience has grown an individualism which I predict can and will play a vital part in shaping our future. I make no apology for selecting "Individualism" as the title for these remarks.

It was along in 1932 that the most recent edition of "The Forgotten Man" first made his appearance. I have no quarrel with him, nor with his equally vague brother of an earlier generation, "The Common Man." His advent did not indicate any strange obstetric phenomenon, although it did bear the earmarks of a political conception. History has recorded similar conceptions. The only serious fault I have to find is the shallow thinking which seeks to put a premium on mediocrity—for a political consideration. Now we have reached the point where both the "forgotten" and the "common" man resent these designations and both find themselves challenging the very political thinking which created them, with results which merely accentuate the general confusion.

Mediocrity has a way of infiltrating all walks of life. The fear of rising above the crowd, of being different, is not a characteristic alone of the "bobby-sox" brigade, of women who follow bizarre styles in hats, of politicians or of preachers; but it has a way of infiltrating even the medical profession! The tragedy lies in the fact that, when we sink to the level of mediocrity, we lay ourselves open to that next step in mass psychology, regimentation.

Maybe, sometime during the past five years, you have heard the word, "regimentation," applied to our profession! We have been attacked by those who would add to the self-imposed discipline which we cheerfully accepted in time of war, a discipline which no American, worthy of the name, will tolerate; a discipline which would regiment our profession into the position of subservient employees of a bureaucratic state. If we completely attain this low estate, now being so thoughtfully prepared for us by a host of starry-eyed professional "doers of good to people," we will, indeed, come to know both the "forgotten" and the "common" man, for his dual and dull personality will dwell in us.

This is not a pleasing prospect, nor do I believe that it is necessary. But I believe that it is inevitable unless we think and act clearly along some rather definite lines. It seems so difficult for us to grasp the most obvious truth! Some two thousand years ago, the Master of men stated, "He that would be great among you, let him be as your servant." That was, and still is, a challenge to the individual. There can be no finer or more fitting motto for individualism as represented in our ranks than this. No group, no profession throughout the world, has a greater right to adopt that motto than has the medical profession of America.

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*Fourteenth Annual Meeting*

*Chicago, Ill., Sept. 19 to 21, 1946*

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## PRESIDENTIAL ADDRESS\*

### Individualism

JOHN H. MOORE, M.D., GRAND FORKS, N. D.

WHEN I took office as your president in 1941, I was deeply appreciative of the honor you had given me. This Association occupies a unique position in our specialty. While it is the largest Association of Obstetricians and Gynecologists in the country, and while its ever lengthening list of applicants for membership attest its popularity, mere size and popularity do not explain its importance. That importance, it seems to me, lies in qualities much deeper; qualities of mind and heart, placed there by its founders; qualities of intellect, insight, and idealism that have grown with the years and, even in the confusion and chaos of the years of war, have not been lost.

I hope that never again will it be necessary for this Association to have one president as long as it has had me! Charge that also to the destruction and desolation wrought by war! You charged me, along with the other officers and members of the Executive Committee, with the responsibility of keeping this Association alive during those trying years. We have done so. Not only have we kept it alive, but we have strengthened it so that its prestige has grown, its financial condition is sound, its ability to produce sound, sensible, and scientific contributions to obstetric and gynecologic literature has never been higher, and its good fellowship, always a noteworthy feature of our Association, remains pre-eminent. Your executive committee has been most faithful in carrying out its trusteeship by its attendance upon annual meetings even though time was limited, travel difficult and personal expense and inconvenience, considerable.

The founders of the Central Association of Obstetricians and Gynecologists were men of vision. They were individualists and, sometimes, their individual-

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\*Delivered at the Fourteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Chicago, Ill., Sept. 19 to 21, 1946.

in obstetrics and gynecology. Just how heavy that load will be no one seems to know at the moment, although it has long since exceeded the ability of teaching institutions to carry it. Here is a challenge that this young association of specialists cannot and should not avoid. Some of you faculty members in our teaching centers will have to continue to work overtime to train men who can follow you; others in private practice should make places available for training by preceptorship, subject to the requirements of the American Board of Obstetrics and Gynecology. This must remain an individual problem.

We have all heard it said, repeatedly, that there are not enough specialists in obstetrics and gynecology to meet the needs of our women for specialist's care. We have also heard much about the inadequate and the uneven distribution of physicians. This is one of the arguments that has been used to force some scheme of socialization of medical practice upon us. I do not believe that the day will ever come when you will find doctors returning to the small villages of my rural State, or to any other, and I do not think that it is economically or socially sound to expect them to do so. With the advent of good roads and modern transportation, the development of adequate facilities for the care of the obstetric patient has already improved greatly in the smaller cities and in the larger towns in our rural areas. It is not necessary to subsidize or otherwise try to inveigle doctors into such areas. A proper system of preceptorships set up under conditions of free enterprise that are attractive to our thoughtful young prospective specialists will result in a more equitable distribution of those specialists in obstetrics and gynecology.

Individualism must possess or develop insight into the social, economic, and political problems that perplex the medical profession as it attempts to carry on the American tradition of free enterprise in medical practice. Emotionalism has no place in a critical approach to the sociologic problems confronting us in the practice of medicine in postwar America. We should have learned that lesson during the war years. The great shifts in population from rural to urban areas during those years, now the shift toward decentralization, have confused us. No one liked the E.M.I.C. program less than I. But the emotional outbursts against it by certain members of our profession only served to illustrate the futility of such action. The Children's Bureau, opportunely, created an emergency. That alleged "emergency" is past but I do not see that there has been any lessening of the "emergency" in the minds of those who desire a continuing bureaucratic control of the practice of obstetrics!

We have not effectively presented the case of free enterprise in obstetric practice to our patients. Our childbearing public is all through shedding tears over the heroic (?) delivery by lamplight in the kitchen of an isolated farm home. They want to know why, in a so-called modern world, such a situation should ever become necessary. This is a social problem. We have an individual responsibility to direct the social planning for the future along the constructive lines of free enterprise. If the emphasis is to be placed where I believe that it belongs, upon decentralization in government, then in the medicosocial aspects of this question we need to have the insight to direct that decentralization upon sound lines. In an imperfect society, there will probably always be those



Individualism does not come through mass production or the assembly line, and yet it has made those contributions to American industry possible. In whatever field you find it, but particularly in our own, it is an aristocracy of intellect, insight, and idealism. It is and must remain individualistic to satisfy those rigid requirements for greatness, enunciated so long ago.

The aristocracy of intellect is placed first because no man can serve greatly who has not an orderly, a disciplined, a trained mind. There is danger that an aristocracy of intellect can become cold, calculating, cynical, and cruel, but not if the individual belonging to it has the real elements of greatness within him, a humble searcher after truth linked with a desire to serve. Lest I be classed as a misguided visionary, let me give you the Twentieth Century Dictionary's definition of intellect: "That faculty of the human soul or mind which receives or comprehends the ideas communicated to it by the senses, or by perception, or by other means; the faculty of thinking; the understanding."

It has always been traditional with medicine that its discoveries have been widely disseminated for the good of all. The horrors of Belsen and Buchenwald, where barbaric torture and wanton destruction of helpless human lives were practiced under the guise of experimental medicine, violated every approach to intellect and descended to depths of depravity which would be almost unbelievable were not the documentary proofs so damningly convincing. Here were not orderly, disciplined, trained minds at work; minds united in a great, yet humble search for truth, but diseased and degenerated dupes of a once free profession whose very souls had been sold to the implacable hatred of a dissolute state. A cold, calculating, cynical, and cruel intellect can come only when the dignity of the individual is destroyed. Then the faculty of thinking is taken away and the understanding heart is stilled.

By contrast, one needs only to think for a moment of the contributions which a free profession made to the winning of the war and, we hope, to the preservation of the peace, to realize that the aristocracy of intellect, unhampered in the field of medicine, can literally bring men back from the jaws of death. But these lifesaving gifts were offered by a medical generation whose talents, very largely, had been developed during days of peace. This generation of physiologists, biologists, and clinicians began its work under conditions of peace. What is not so generally appreciated just now is that there has grown up a medical generation that has not had the opportunity to stimulate the intellect. They were rushed through an already crowded medical curriculum, given a few months of inadequate intern training, and sent to fill the ranks of medical officers in the Armed Services. They served courageously, and many of them died heroes' deaths. But with all honor possible given to this fine group of young men, the stubborn fact remains that we have lost a medical generation. With all due credit to the tremendous contributions that war medicine has made to the control of epidemics, the combating of shock, the prevention of wound infections, the rehabilitation of the disabled, the fact remains that our own specialty of obstetrics and gynecology has marked time. Teaching institutions lost many of their key men, as well as their residents and fellows in obstetrics and gynecology, to say nothing of their interns. Now, many of these younger men are returning from military service, eager to resume their special training

stances of things not seen," worked out their mathematical formulas with a high degree of faith and, finally, on an August day in 1945, the world suddenly learned in an awful manner just a little more about a new age that had dawned. Now we know that the future of civilization rests with the idealists who will control it. This has always been true, but it will require individualists with idealism to make that future secure.

This demands an awakening of the sense of our individual responsibility to our fellow men. The idea is not new. The ancient prophet, Micah, disgusted and disheartened by the limited vision of his generation, summed it up when he said, "He hath showed thee, O Man, what is good. And what doth the Lord require of thee but to do justly and to love mercy and to walk humbly with thy God."

As we renew our annual meetings together, as we go about our daily tasks, as we face the difficult problems that lie just ahead in our social, economic, political, and professional relationships with our fellow men, let us take a large measure of idealism with us. That, with intellect and insight, will develop the individualism which is so desperately needed at this hour.

Frank Mason North, in his beautiful poem, caught the spirit of what I have been trying to say when he wrote:

Where cross the crowded ways of Life,  
Where sound the cries of race and clan,  
Above the noise of selfish strife,  
We hear Thy voice, O Son of Man!

In haunts of wretchedness and need,  
On shadowed thresholds dark with fears,  
From paths where hide the lures of greed,  
We catch the vision of Thy tears.

From tender childhood's helplessness,  
From woman's grief, man's burdened toil,  
From famished souls, from sorrow's stress,  
Thy heart has never known recoil.

The cup of water given for Thee  
Still holds the freshness of Thy grace;  
Yet long these multitudes to see  
The sweet compassion of Thy face.

O Master, from the mountain side,  
Make haste to heal these hearts of pain,  
Among these restless throngs abide,  
O tread the city's streets again,

Till Sons of Men shall learn thy love  
And follow where thy feet have trod  
Till glorious from Thy heaven above  
Shall come the city of our God.

In this spirit, I summon you to an individualism worth while; to the aristocracy of intellect, insight, and idealism.

who are indigent. Whatever the cause of their indigency, they must have medical care. The social implications of that care are tremendous. These unfortunates are the financial responsibility of the State, of you and of me as members of that State. Let us assume that responsibility by decentralizing it as much as possible for humanitarian reasons; and when local responsibility is placed, let us assume our individual responsibility by caring for the indigent mother as carefully and as conscientiously as we would care for her more socially fortunate sister. If federal funds are necessary to augment local resources in maternal care to the indigent, then let those funds be locally administered, and let us be sure that whatever local agency administers them retains and strengthens the personal relationship between patient and physician.

Individually, we must improve our political relationships if we are to develop that insight which is so necessary to our profession today. In my opinion, it is high time that we acquired political importance in matters pertaining to the health of our citizens. Such importance doesn't start in Washington. It begins in your ward and in mine. It extends onward through municipal, county, and state governments and, finally, if intelligently used, it may become effective in Congress. I have a very high regard for the Congress of the United States. I believe that, in matters of health and welfare, they are earnestly trying to work out an equitable solution to a very complex problem. How much have we helped them? Oh yes, when we have reached a sufficient degree of emotionalism regarding the E.M.I.C. program or the Wagner-Murray-Dingell Bill we have sporadically written or telegraphed them our views. But have our protests had much constructive, positive thinking back of them, or have they been largely negative? Have we had an objective approach to these great questions of maternal care, the distribution of medical care, voluntary health insurance plans, full-time health units, and many related problems? Politically and objectively these are local in origin, and we must recognize that fact and proceed accordingly if our influence is to be at all effective. We need a grass-roots organization of individualists whose constructive and objective thinking on what is best for the American mother and her baby will have political foresight and direction emanating, if you please, from our own back yards!

By some, idealism may be considered synonymous with the visionary, the fanciful, the unreal. But in individualism, as I have tried to picture it, it has a spiritual basis. This antonym of realism is what men live *for*. Without it, life becomes a long series of Tobacco Roads. Gradually it is dawning upon us that, truly, only those "things which are not seen" are eternal. *It is being driven home to men everywhere that the Sermon on the Mount is the only defense against the atomic bomb.* We move in cycles in our thinking. We have prided ourselves upon our realism in literature, the arts and industry and a "realistic approach," whatever that may be, was urged upon us in religion. But let us stop, take stock of ourselves, and see if realism and idealism have anything in common. They have, at least at one point; both search for truth. I think that we can all agree that the basic idea for the splitting of the atom, with its infinite possibilities for human destruction or for human betterment, did not originate in the minds of realists. Idealists dreamed dreams, speculated on the "sub-

"delayed," as Rockstroh has called it, rather than "irregular" shedding, and we believe that the concept of this disorder could be more readily grasped by the undergraduate medical student if some more striking term were substituted for the colorless word "irregular." While "delayed" appears to be an improvement, it obviously is not all that could be desired. However, lest we unnecessarily confuse the picture even before this diagnosis is widely established, we have decided against any attempt to improve upon the term previously employed by the vast majority of investigators.

In this country numerous papers have dealt with the subject of functional uterine bleeding, but few have been concerned with endometria exhibiting the characteristics of irregular shedding. Traut and Kuder (1935) described both irregular or incomplete shedding, an aberration of the secretory phase of the cycle, and irregular ripening or maturation, representing a mixture of both proliferative and secretory phases. Irregular ripening was characterized by bleeding in the midportion of the menstrual cycle (metrorrhagia) and the endometrium suggested a patchy or irregular corpus luteum effect superimposed upon the proliferative phase. We have not encountered metrorrhasias presenting this particular histologic picture, and we are at least mildly skeptical concerning the reality of such a clinical entity since we have made an earnest endeavor to classify by histologic means every patient relating any derangement of the menstrual cycle. Traut and Kuder emphasized that irregular shedding and irregular ripening had been neglected by students of uterine bleeding although in their experience these disorders accounted for approximately one-third of all functional uterine bleeding. Hamblen (1939, 1945), recognizes that abnormal bleeding (menorrhagia) can occur from progesterational endometria, but he has not seen fit to dignify this situation with a specific diagnostic title. In his monographs he refers briefly to irregular shedding of the endometrium, but considers it a minor variation of normal menstruation. Jones (1938) discussed functional uterine bleeding associated with secretory endometrium, but concluded that the patients studied had "no characteristic menstrual history" and that the endometrium of irregular shedding, as described by others, had no peculiarities which would allow it to be set apart as a pathologic entity. Wilson and Kurzrok (1938) made brief mention of Traut's "irregular ripening," but decided to exclude any such disorder from their concept of mixed endometria. Apparently they were not at all impressed by the possible importance of irregular shedding. Strangely enough, these investigators had never encountered an endometrial section which suggested the persistence of an actively secreting corpus luteum beyond a period of fourteen days. Israel and Mazer (1938), on the other hand, were prepared to admit that irregular shedding of the functional layers of the endometrium might be the immediate cause of prolonged or excessive bleeding. Mann and his associates (1942) indicated a familiarity with Traut's description of irregular shedding but, for reasons which were not disclosed, felt that such an entity could not be fitted into any physiologic or pathologic scheme "except by some tortured interpretation."

In 1940, Sturley reviewed an experience with seventeen cases of irregular shedding seen at the University of Minnesota Hospital. Two years later McKelvey (1942) presented a brief general survey of the problem and a preliminary report on 36 patients observed in the same clinic. Recently Professor McKelvey has very kindly permitted us to read in manuscript form a paper dealing extensively with the same material. With minor exceptions, his observations have paralleled our own as set forth below. He suggests that the pathologic findings in the endometrium may be linked in some way with persistence through more than one menstrual cycle of thick-walled spiral arterioles. His urinary

# MENORRHAGIA ASSOCIATED WITH IRREGULAR SHEDDING OF THE ENDOMETRIUM\*†

## A Clinical and Experimental Study

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WE EMPLOY the phrase irregular shedding of the endometrium to indicate a specific type of functional uterine bleeding which is characterized by prolongation of cyclic menstrual bleeding from progestational endometrium and often, in addition, by an increase in the amount of bleeding. The diagnosis is suggested by the typical clinical history of regularly recurring menorrhagia, and may be substantiated by recovering secretory endometrium by curettage during the course of the prolonged bleeding, but well beyond the time when endometrial regeneration normally would have occurred.

Although gynecologic literature contains numerous references to irregular shedding of the endometrium, this important clinical and pathologic syndrome has not been accorded the recognition it deserves. Any mention of it is noticeably lacking in the latest textbooks. We propose to show the frequency with which this diagnosis may be employed to explain menorrhagias, providing only that histologic material be obtained from the uterus at the proper time in the menstrual cycle. The characteristic clinical picture will be presented, and the microscopic findings in the endometrium will be described in detail. The results of attempts to reproduce this disorder in normally menstruating women will be shown, and a tentative explanation of the etiology of irregular shedding will be offered.

Much of the early literature has been covered adequately by Jones (1938) and also by McKelvey (1942). The earliest reference to a condition which fits our present concept of irregular shedding was that of Driessen (1914) who described prolonged and incomplete shedding of the endometrium associated with cyclic bleedings. Jones has summarized the papers of Pankow (1924), Kaufmann and Hoeck (1927), and Banicki (1928), and it seems unnecessary to restate their contributions here. Robert Meyer (1930) included a complete description of irregular endometrial shedding in the uterine volume of the Henke-Lubarsch handbook and Rockstroh (1938), working in Meyer's laboratory in Berlin, reviewed at length the pathologic anatomy and clinical findings of what he called "delayed" shedding. He assumed that delayed shedding resulted from an insufficient production of estrin, and treated eight patients with an oral estrogenic preparation early in their menstrual cycles. The results were inconclusive. There is much to be said in favor of the use of the term

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While bleeding from the human uterus at the time of normal menstruation ordinarily lasts from four to seven days, there is rather general agreement that the actual shedding of endometrial tissue is complete within two to four days. Novak and TeLinde (1924), after examining uteri removed during menstruation, concluded that shedding was very extensive by the second day, and regeneration of surface epithelium from stumps of uterine glands was conspicuous on the third day. More recently, Novak (1940) has set the third day as the time when desquamation has commonly reached its limit. Bartelmez (1933), in a study of 17 surgical specimens subjected to immediate fixation, described and illustrated endometrial repair appearing early on the fourth day after the onset of menstrual bleeding. Herrell and Broders (1935) stated "there can be no doubt that loss of tissue is complete in the first twenty-four hours of menstruation, and that the remainder of the menstrual period is one of hemorrhage and secretion." Campbell and his associates (1936) also concluded that the stage of tissue loss is brief, lasting not more than one or two days, and that before it is completed re-epithelization has already begun.

From these observations, and on the basis of our own studies of normally menstruating women, it would seem reasonable to conclude that the shedding of secretory tissue ordinarily is completed within forty-eight to seventy-two hours after the onset of bleeding. Regeneration of a new surface occurs rapidly thereafter, and by the fourth or fifth day of the cycle one almost routinely observes new proliferative endometrium. Fig. 1 shows a section of endometrium obtained by curettage from a 22-year-old normal woman who had a regular cycle of twenty-five to twenty-eight days, with bleeding lasting five to six days. Curettage was done on the fifth day of bleeding. Note complete regeneration of the surface epithelium and early proliferation changes in the glands.

We should not expect to find on the fifth day of menstruation comparatively large areas of secretory glands belonging to the previous cycle. This finding, coupled with a characteristic clinical history of menorrhagia, has been our criterion for the diagnosis of irregular shedding of the endometrium.

### Pathology

The salient pathologic feature of the disease is that the endometrium remains in menstrual decomposition over a prolonged period of time. As mentioned above, in the normal cycle the shedding of the menstrual endometrium is usually completed in two days, and regeneration of the surface epithelium is complete by the fifth day. In the typical case of irregular shedding of the endometrium, the process of shedding will still be occurring on the fifth day of bleeding or even later. In order to make the diagnosis, curettage material must be obtained at the time when it will show the most characteristic findings, namely, on the fifth or sixth day of bleeding. Also, the pathologist must interpret the findings in relation to the menstrual history. Endometrium obtained on the first day of a normal cycle will show many of the characteristics of endometrium obtained from a case of irregular shedding on the fifth day. Failure to appreciate this fact has, we believe, been the chief obstacle to a wider recognition of the disease process. Endometrium obtained at the proper time in the cycle will show the following characteristic findings: There is marked irregu-

excretion studies, carried out in six cases, indicated that pregnandiol was excreted during the menstrual bleeding, contrary to the usual finding, and from this it was inferred that irregular shedding might be a specific endocrinologic entity.

### The Histology of Normal Menstruation

We employ the term menstruation to designate uterine bleeding associated with the shedding of an endometrium which has manifested secretory or progestational changes. To justify our contention that irregular shedding of the endometrium is an abnormal condition, a brief review of the events in normal menstruation seems desirable at this point. The various aspects of menstruation have been covered exhaustively by Schroeder (1928), R. Meyer (1930),

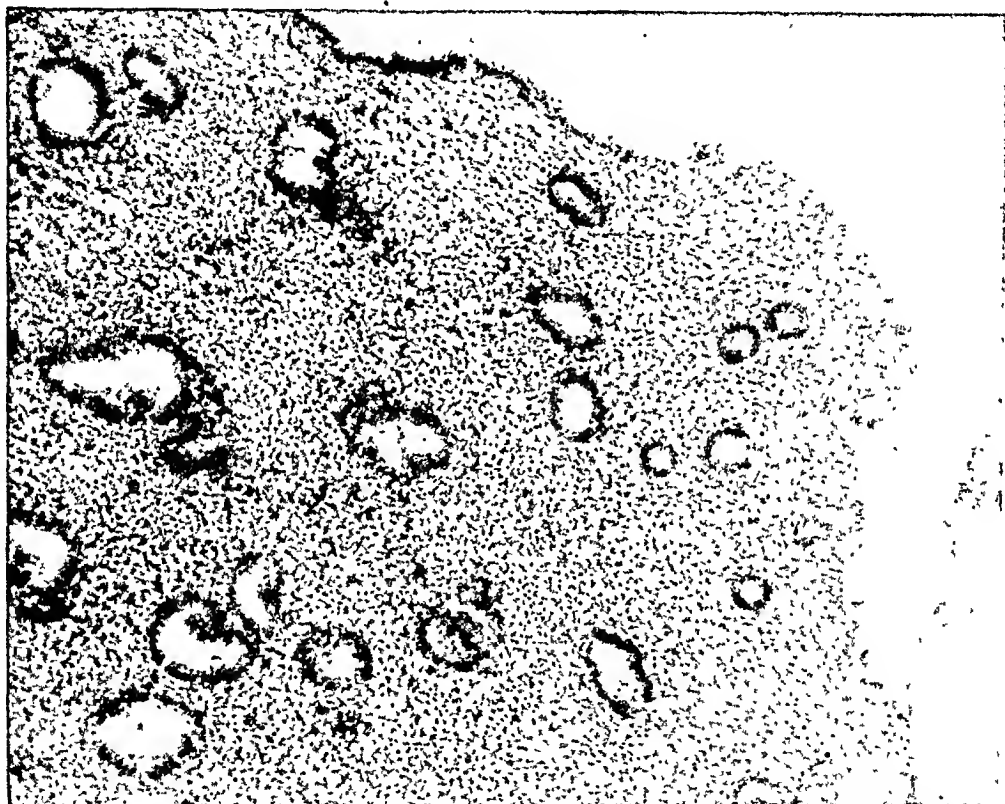


Fig. 1.—Curettage material obtained on the fifth day of normal cycle. Surface reformed, glands in early proliferation stage.

and Bartelmez (1937, 1941). The corpus luteum presumably ceases to function one or two days before the onset of menstruation, and, consequently, the excretion of pregnandiol, formed from progesterone, terminates with the appearance of bleeding. The vascular changes appearing in the spiral arteries of the functionalis at the beginning of menstruation have been observed in vivo on ocular transplants in the Macaque by Markee (1940). Constriction of these vessels occurs twenty-four hours before the appearance of hemorrhage. There is marked blanching of the mucosa, a reduction in size of the transplant, then arteriolar dilatation and extravasation of blood. Hematomas form, and finally bits of tissue become detached from the surface in regions where hemorrhage has occurred.



TABLE III. DURATION OF BLEEDING

7 to 9 days	6 cases
10 to 15 days	15 cases
Over 15 days	1 case

TABLE IV. LENGTH OF MENSTRUAL CYCLE

Less than 25 days	4 cases
25 to 30 days	11 cases
Over 30 days	7 cases

Any statement as to duration of bleeding is of necessity an approximation, for many times there was a variation of as much as four days from period to period. Some criticism might be leveled at designating a period of bleeding lasting seven days as prolonged. Nevertheless, the increase of length of flow up to seven days represented a distinct change in the menstrual habits of these patients, and prompted them to seek medical advice because of the change.

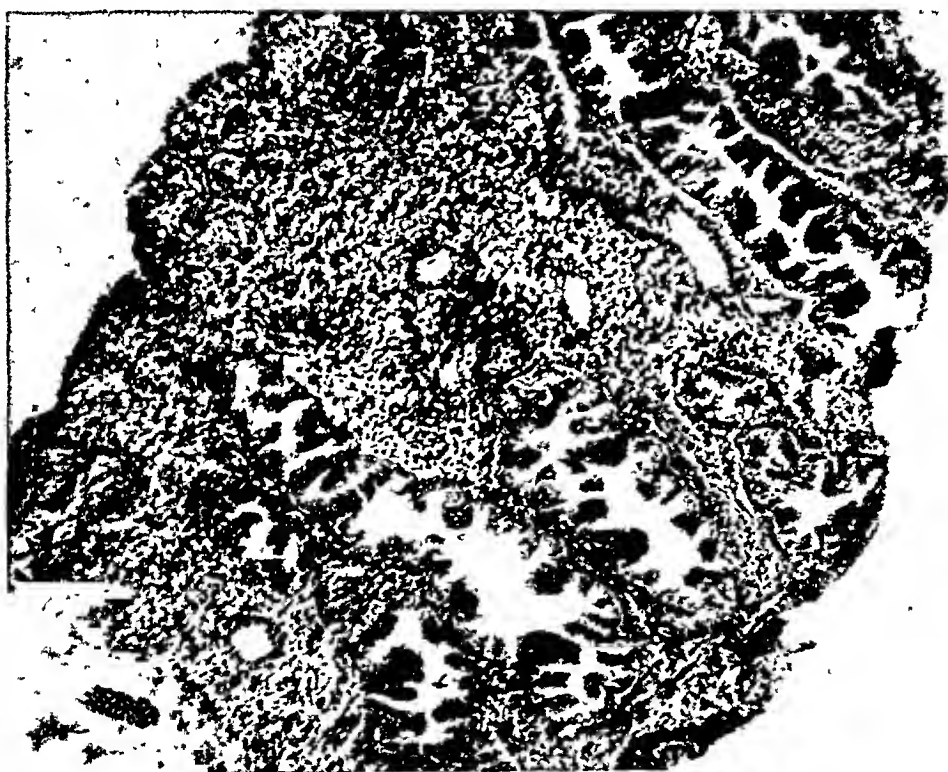


Fig. 2.—Case 1. Endometrium removed on sixth day of bleeding, showing marked retention of secretory glands, overdevelopment of stroma.

There seems to be no correlation between the duration of bleeding and the length of the menstrual cycle. One patient, who had periods of bleeding lasting fifteen to twenty days out of each cycle, still could predict the onset of her next bleeding, and the cycles were thirty days in length. Another patient, who had periods of bleeding lasting twelve days, had a cycle which was regularly twenty-four days in length.

Space does not permit a discussion of all of the cases which make up the material for this report. In order to demonstrate the nature of the problem, three cases will be reported in detail and microscopic sections from five additional cases will be shown.



larity in the thickness of the endometrium. The surface epithelium is missing. The stroma is shrunken and composed of many deeply basophilic nuclei with little cytoplasm. The glands are collapsed but show evidence of secretion change. Most of the secretion of the cells has been discharged. The lumina appear star-shaped when cut in cross section as a result of collapse and shrinkage of the surrounding stroma. Many arterioles near the surface are dilated and have a thicker wall than is usually seen in this portion of the endometrium. These points will be stressed again in the presentation of the clinical material below.

In the interpretation of this material, it must be borne in mind that these areas of endometrium belong to the previous cycle. Although retained for abnormally long periods of time, the tissue is gradually cast off. The normal mechanism of regeneration is continuing through this period in an irregular fashion, and is apparently able to catch up before the next ovulation occurs in at least a large proportion of the endometrium. Therefore there is usually no change in the length of the cycle over the normal.

### Clinical Material

During a period of three years, uterine curettage was carried out on 242 patients in the Salt Lake General Hospital. A pathologic diagnosis of irregular shedding of the endometrium was made in 22 of these. The diagnosis was also made in several additional instances, but the bleeding abnormality in these cases was so closely associated with a recent abortion that these were thought to be more properly labeled as postabortal subinvolution of the endometrium, and are therefore not included in the present report. This was substantiated in follow-up studies of the postabortal cases, all of whom had no recurrence of the bleeding abnormality following curettage, whereas many of the cases of true irregular shedding had no relief from curettage or were ultimately treated by surgical intervention. A breakdown of the 22 cases from a standpoint of age incidence, parity, duration of bleeding, and length of the cycle is of interest.

TABLE I. AGE INCIDENCE

20 to 30 years	11 cases
30 to 40 years	8 cases
40 plus years	3 cases

TABLE II. PARITY

0	2 cases
1-11	20 cases

This is of particular interest in view of the fact that previous authors have reported the highest incidence of the disease near the age of the menopause. The cases which have proved to be the most refractory to treatment and which have posed the most difficult problems in our experience have been those in the early age group. Three such cases will be discussed in detail below.

The preponderance of cases in women who have had pregnancies cannot be overlooked as a possible clue to etiology. In half of our cases, the patients also dated the onset of the abnormal bleeding to a pregnancy.

CASE 2.—V. J. (Hosp. No. 2117), aged 23 years, para ii. First seen in September, at which time she complained of prolonged periods of vaginal bleeding for the preceding three months. Her last pregnancy was two years previously. Menses occurred at intervals of thirty days, but flow was prolonged up to fifteen to twenty days. Previously, flow had never been more than six days in duration. Physical examination and workup revealed no abnormalities aside from an anemia with a hemoglobin value of 10 grams. Pelvic examination revealed apparently normal internal genitals. Dilatation and curettage was done on the seventh day of bleeding. The endometrium showed an excessive secretory change in the glands, marked delay in the shedding of the endometrium, and overdevelopment of the stroma (Fig. 5). Bleeding continued for four days following the curettage. The patient was readmitted two months later with the same complaint. Bleeding period during the interim had lasted for fifteen days.

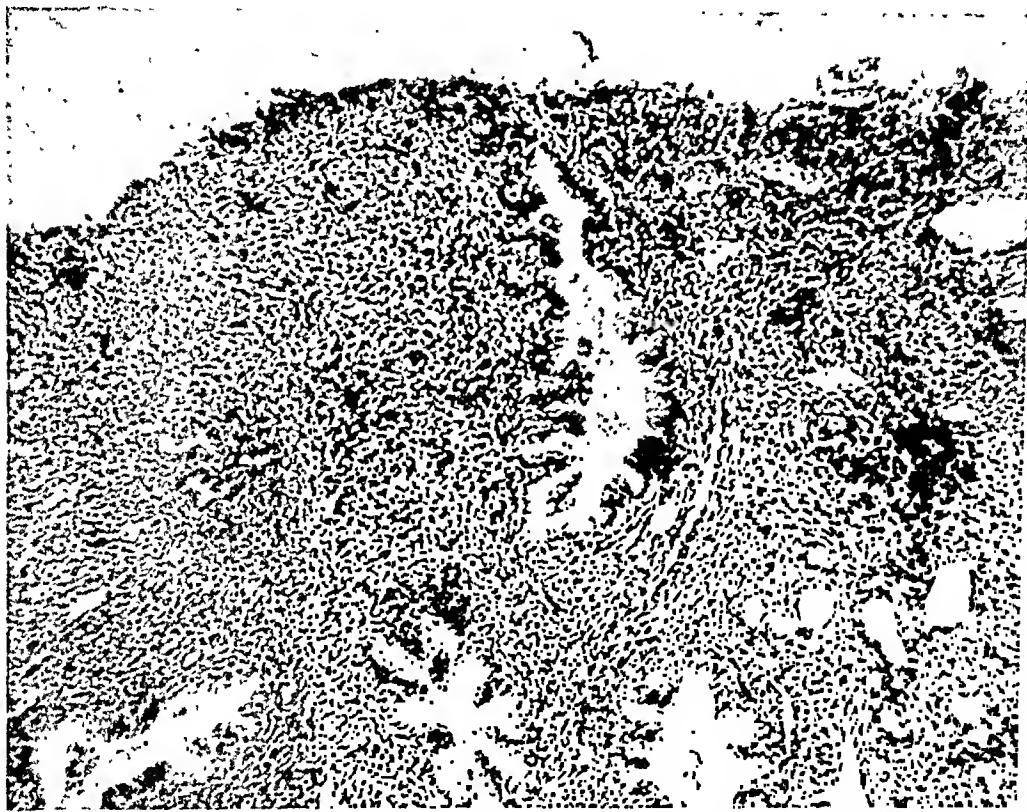


Fig. 4.—Same case as Figs. 2 and 3. Endometrium from hysterectomy specimen obtained on eighth day of bleeding, showing retention of secretory glands, delay in healing of surface.

At the time of admission in November she had already been bleeding for ten days. The endometrium showed marked delay in regeneration. Remnants of old secretory glands from the previous cycle could still be recognized (Fig. 6). The patient was readmitted again on February 11. Bleeding periods meanwhile had been as follows: December 8 to 28; January 6 to 21; February 4 to admission. Beginning on January 29 (twenty-fourth day of last cycle) the patient was given daily intramuscular injections of 10,000 units of estrogenic hormone in oil in an attempt to control the bleeding. This was continued for the next nine days (three days after the onset of bleeding) and was found to have no apparent effect on the amount or duration of the bleeding. On February 13 (tenth day of bleeding) subtotal hysterectomy was carried out. No gross abnormalities were found either in the uterus or the appendages. Sections taken

CASE 1.—M. S. (Hosp. No. 8362), aged 25 years, para ii, was first seen in January with the complaint of prolonged periods of vaginal bleeding since the birth of her last child three years previously. Cycles were regular every 28 to 32 days, but flow was very profuse and lasted for fourteen days. Last period of bleeding before admission was from December 22 to January 4. Pelvic examination revealed no abnormalities. Curettage was carried out on the sixth day of the next bleeding which began on January 23. Examination of the curettage material showed marked retention of the secretory phase endometrium from the previous cycle (Fig. 2). The next period of bleeding began on February 25. Endometrial biopsy was obtained on the fifth day of bleeding.

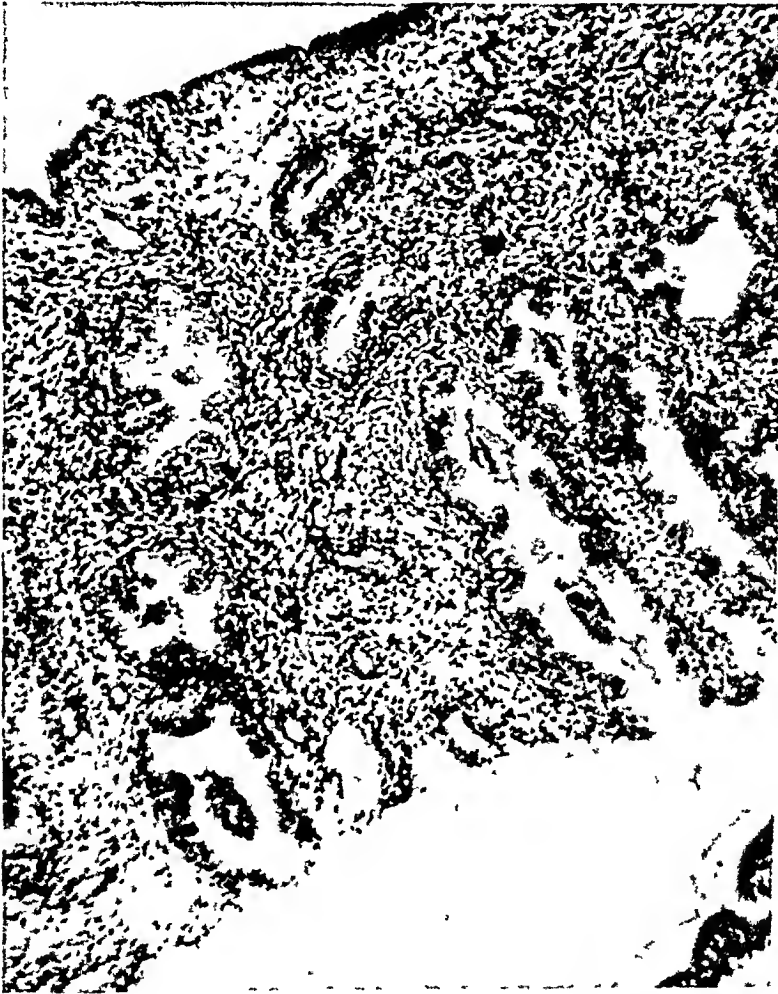


Fig. 3.—Same case as Fig. 2. Endometrium removed on fifth day of next menstrual cycle.

Examination of this tissue showed a picture similar to that obtained by curettage (Fig. 3). Bleeding continued for an additional nine days after the biopsy was taken. Pelvic examination on April 7 revealed the presence of a 6 cm. cystic mass in the region of the left ovary. This was thought to represent a follicle cyst of the ovary. On the eighth day of the last bleeding a subtotal hysterectomy was carried out, together with removal of the left ovarian cyst, which proved to be only a cystic follicle. Sections through the uterine wall showed scattered areas of adenomyosis. The endometrium again demonstrated delay in shedding and lack of healing of the surface even though the uterus was removed on the eighth day of bleeding (Fig. 4).

through the uterus again showed a delay in the shedding of the endometrium from the previous cycle and little evidence of regeneration. Large blood vessels, some of which were thrombosed, could also be seen on the endometrial surface (Fig. 7).

CASE 3.—J. H. (Hosp. No. 1679), aged 31 years, para vii, was first seen in January. She stated that her periods had been regular and lasted for six days up to birth of her last child in the previous February. Since that time menses had continued to recur at intervals of twenty-four days, but flow was prolonged up to 12 days. Examination on admission showed presence of a chronic anemia (hemoglobin 11 grams), splenomegaly and hepatomegaly, no pelvic abnormalities.



Fig. 7.—Same case as Figs. 5 and 6. Endometrium from hysterectomy specimen obtained on tenth day of bleeding. There is delay in endometrial growth. Note large thrombosed vessel near the surface.

Complete workup by the Department of Internal Medicine indicated that the splenomegaly and hepatomegaly were associated with the hypochromic anemia which was thought to be due to chronic blood loss. Curettage was done on the fifth day of bleeding. The endometrium showed retention of secretory glands from the previous cycle, delay in healing of the surface, and the presence of large blood vessels in close proximity to the secretory glands (Fig. 8). The patient was readmitted in July with the same complaints. Since the previous curettage, the patient had continued to bleed at intervals of twenty-four to twenty-six days with profuse periods of bleeding lasting ten to twelve days. Curettage was repeated on the sixth day of bleeding. The endometrium showed a similar picture to that obtained previously (Fig. 9). Patient was readmitted for the third time in December, 1945, with the same complaints. The anemia had not responded to therapy. Hemoglobin on admission was 8.8 grams. The Department of Internal Medicine urged that hysterectomy be carried out in order to cure the anemia. A subtotal hysterectomy was carried out on the twenty-



Fig. 6.—Case 2. Endometrium obtained on seventh day of bleeding showing retention of secretory glands which are collapsed, compact stroma.

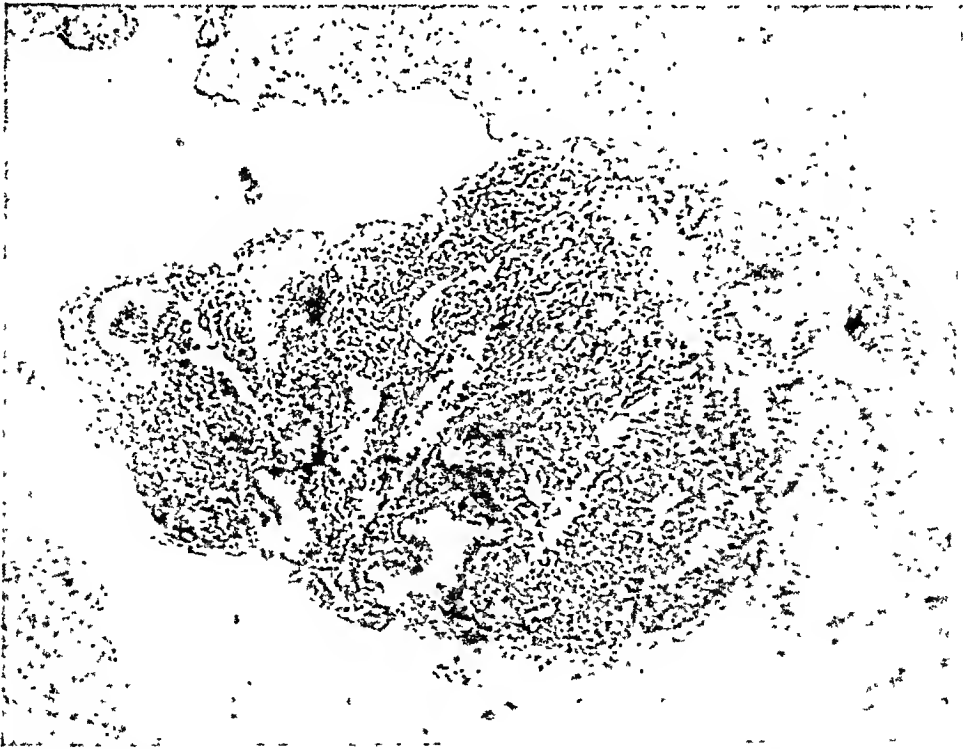


Fig. 6.—Same case as Fig. 5. Endometrium obtained on tenth day of bleeding showing retained secretory glands, delay in regeneration.

second day of the cycle. Grossly, the uterus and appendages presented no abnormalities. Microscopic section of the endometrium showed an excessive degree of secretory change. Even the basal glands in direct contact with the myometrium showed progesterone effect (Fig. 10). This could perhaps indicate an excessive progesterone stimulation which might have an etiologic significance. This possibility is described more fully below. The anemia cleared completely following cessation of the menstrual bleedings.



Fig. 10a.—Same case as Figs. 8 and 9. Section of endometrium from uterus removed on twenty-second day of cycle, showing excessive secretory change in basal glands.

The three cases presented all demonstrate the recurrent nature of the problem. None of these cases benefited from curettage.

Less detailed presentation of an additional five cases will serve to demonstrate further the characteristic histologic features of the disease.

CASE 4.—A. M. (Hosp. No. 6598), aged 38 years, para iv. Complaint: bleeding fourteen days out of each twenty-eight-day cycle. Curettage done on fifth day of bleeding (Fig. 11).

CASE 5.—I. H. (Hosp. No. 9043), aged 45 years, para ii. Complaint: bleeding for twelve days out of each twenty-one- to twenty-four-day cycle. Curettage on fourth day of bleeding (Fig. 12).



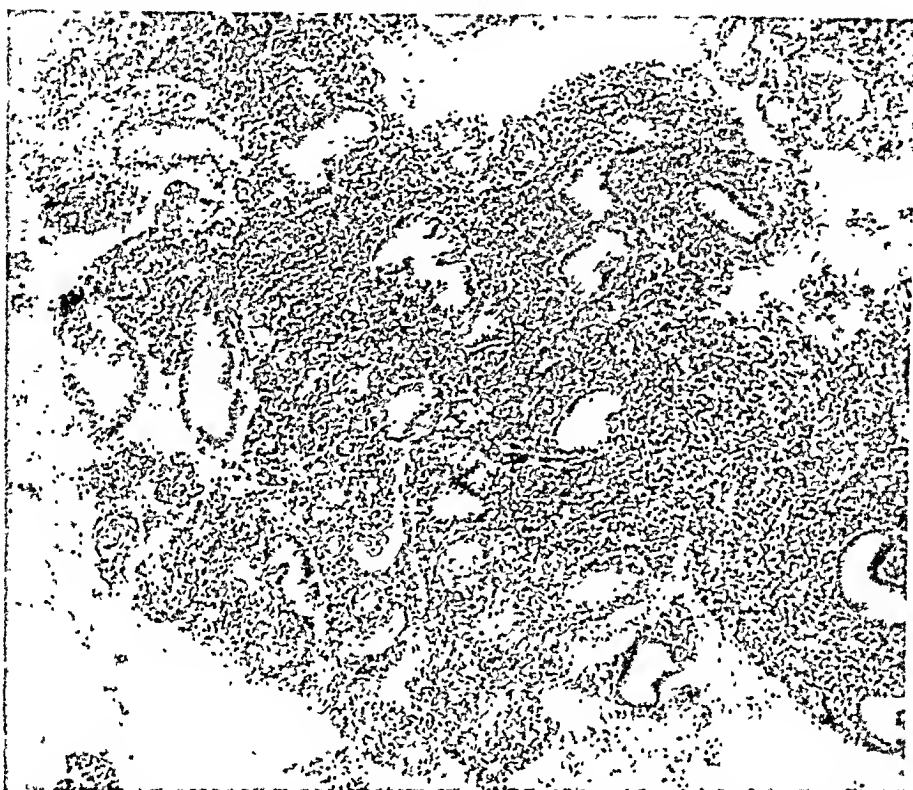


Fig. 8.—Case 3. Endometrium obtained on fifth day of bleeding showing secretory glands from previous cycle, large blood vessels in close proximity to secretory glands.

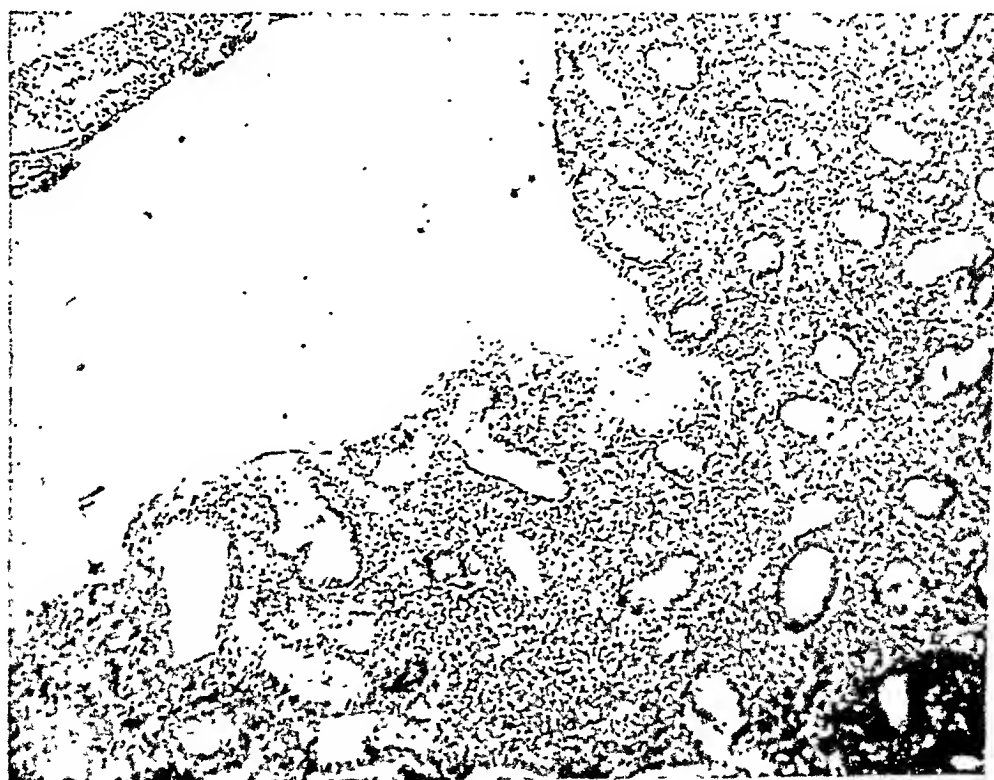


Fig. 9.—Same case as Fig. 8. Endometrium obtained on sixth day of bleeding showing delay in healing of the surface, numerous secretory glands from previous cycle.

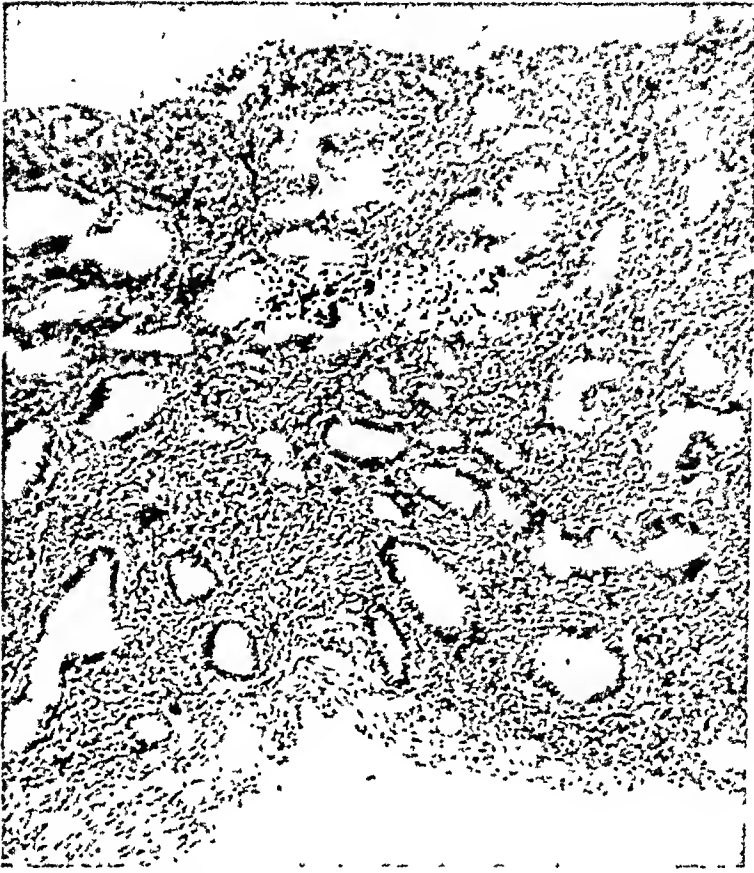


Fig. 12.—Case 5. Endometrium obtained on fourth day of bleeding, showing absence of surface epithelium, retention of secretory glands.



Fig. 13.—Case 6. Endometrium obtained on fifth day of bleeding showing retention of secretory glands.





Fig. 10b.—High-power view of basal glands in Fig. 10a. Note marked evidence of progesterone effect on basal glands.



Fig. 11.—Case 4. Endometrium obtained on fifth day of bleeding showing presence of secretory glands from previous cycle, delay in healing of surface, thrombosed vessels.

CASE 6.—M. B. (Hosp. No. 4688), aged 32 years, para iii. Complaint: bleeding nine days out of each thirty-day cycle. Curettage on fifth day of bleeding (Fig. 13).

CASE 7.—H. F. (Hosp. No. 3870), aged 30 years, para v. Complaint: bleeding for ten to fourteen days out of each thirty-day cycle. Curettage done on sixth day of bleeding (Fig. 14). This patient eventually had hysterectomy performed. The uterus showed the presence of adenomyosis.

CASE 8.—G. P. (Hosp. No. 8392), aged 23 years, para i. Complaint: bleeding for fourteen days out of each twenty-eight to thirty-day cycle. Curettage done on third day of bleeding (Fig. 15). Endometrial biopsy taken on fifth day of next cycle (Fig. 16).

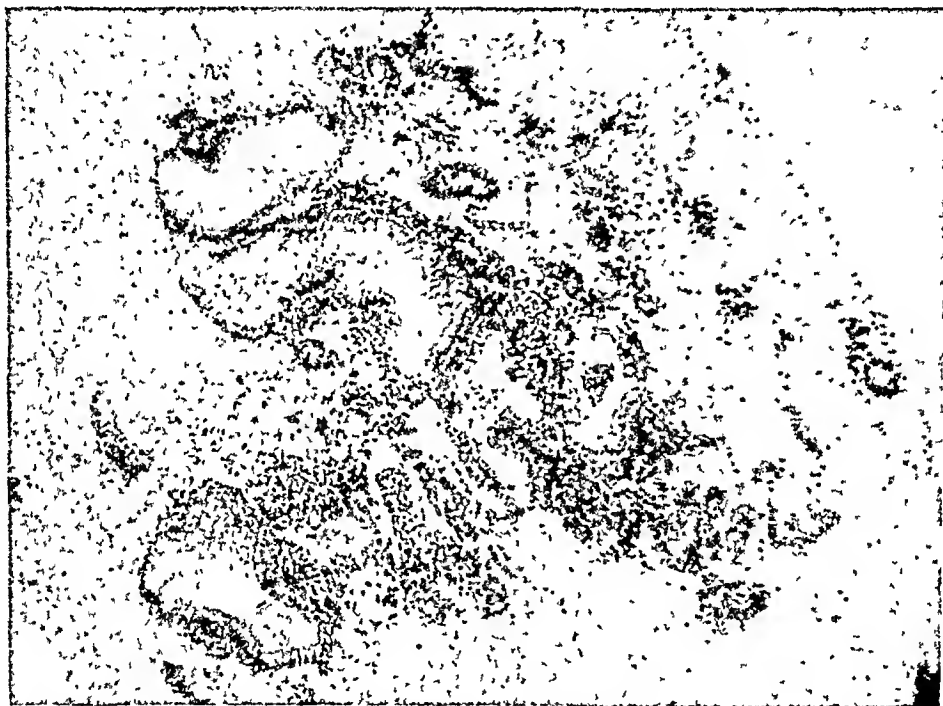


Fig. 16.—Same case as Fig. 15. Endometrial biopsy taken on fifth day of next cycle shows retention of secretory glands.

### Etiology and Experimental Study

There are a number of associated lesions in the uterus and endometrium which may play an etiologic role. The presence of submucous myomas or endometrial polyps may interfere with the normal shedding process. The association of postabortal subinvolution of the endometrium and irregular shedding has already been mentioned. The simultaneous occurrence of adenomyosis and irregular shedding, as demonstrated in two of our cases, may be indicative of a common etiology of the two conditions. However, after these etiologic possibilities have been considered, there still remain a large number of cases in which the etiology is obscure. Our present study is concerned particularly with this group of cases. An attempt has been made to demonstrate a hormonal basis for these. From a theoretical standpoint it would seem that the corpus luteum and its hormone progesterone should play an important



Fig. 14.—Case 7. Endometrium obtained on sixth day of bleeding, showing delay in surface healing, retained secretory glands.

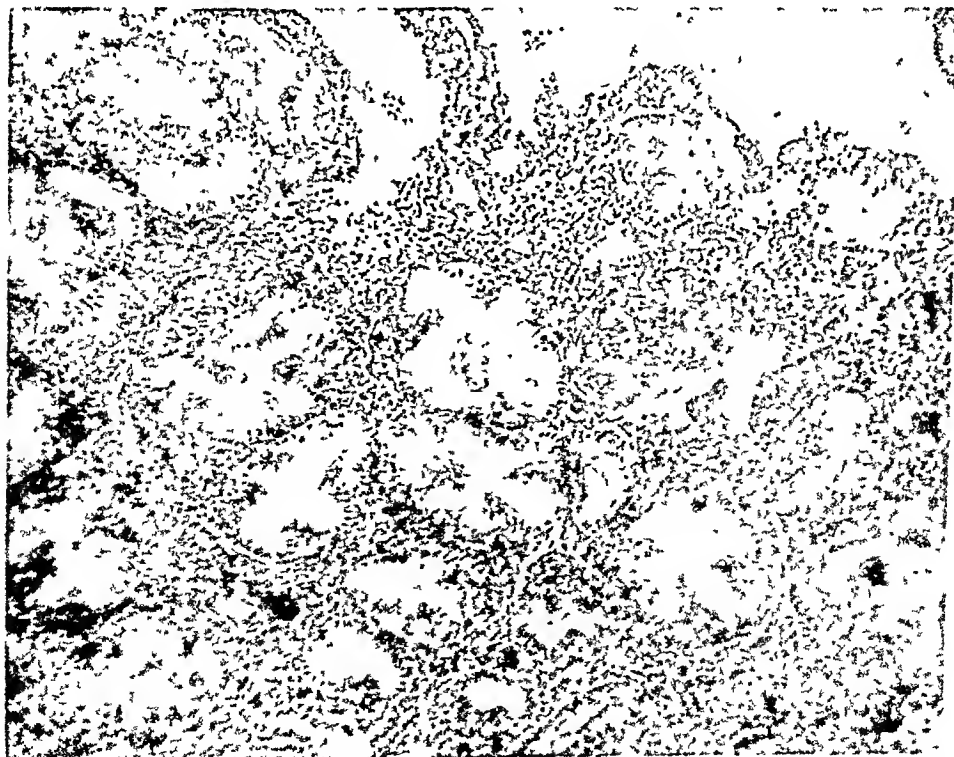


Fig. 15.—Case 8. Endometrium obtained on third day of bleeding. The large, collapsed secretory glands show excessive progesterone effect.

Some studies on patients exhibiting irregular shedding of the endometrium have indicated that they do not follow the normal pattern of pregnandiol excretion, but continue to excrete the substance during the bleeding phase. We have



Fig. 18.—Experimental case 2. Endometrium obtained on the fifth day of bleeding after administration of 10 mg. of progesterone daily beginning on twenty-fourth day of cycle. Bleeding began on the thirty-first day. The glands are in the secretion phase and the stroma has a decidua-like appearance.



Fig. 19.—Experimental case 3. Endometrium obtained on fifth day of bleeding. Beginning on twenty-sixth day of cycle, 20 mg. of progesterone was administered daily until onset of bleeding, which was delayed until thirty-seventh day of cycle. Progesterone was then discontinued. There is no retention of secretory glands, or apparent delay in shedding.

tried to confirm these findings in a small group of cases, but our results have not been consistent enough to draw any conclusions. This investigation is being continued at the present time.

role inasmuch as the outstanding feature of the disease is failure of the uterus to shed endometrium which has undergone progesterone stimulation. This failure may be due to prolonged stimulation of the endometrium by progesterone, i.e., failure of the corpus luteum to undergo prompt and complete regression just prior to menstruation. On the other hand, the defect may be primarily in the endometrium itself, i.e., for some unknown reason there is failure of the endometrium to shed promptly due to an inherent deficiency in the endometrium or its vascular bed. The process of menstruation is inseparably tied up with the blood supply to the endometrium. If the process of constriction of the spiral arterioles and subsequent ischemia is interfered with, it is easy to see how this might influence the normal process of shedding and produce the clinical picture which is so characteristic of irregular shedding of the endometrium.

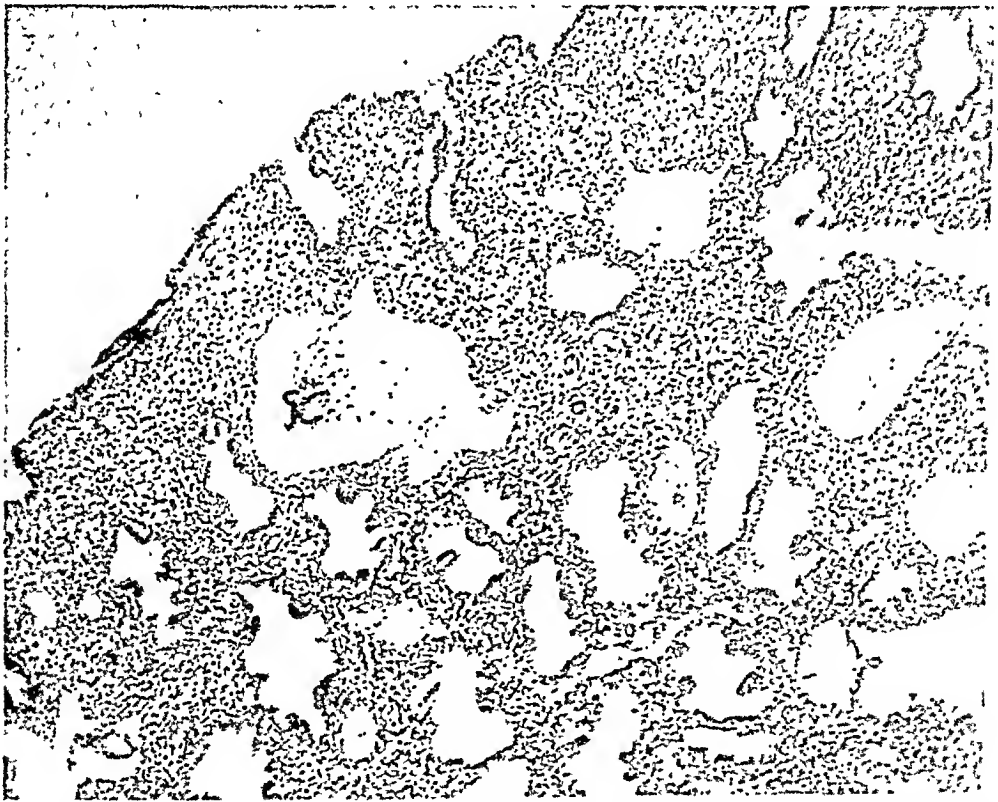


Fig. 17.—Experimental case 1. Endometrium obtained on sixth day of bleeding following administration of 30 mg. of progesterone daily beginning on first day of bleeding. The surface epithelium is intact, and the secretory glands from the previous cycle have not been shed.

The hormonal theory of etiology offers the best opportunity for experimental study. Investigation thus far has been along these lines. Some indication of corpus luteum activity can be obtained by the study of urinary excretion of pregnandiol. Previous investigators have reported the presence of this substance in the urine during the last half of the cycle, with an abrupt drop in the excretion twenty-four to forty-eight hours before the onset of menstruation, paralleling the activity of the corpus luteum. In the normal cycle there is no significant excretion of pregnandiol in the urine during the bleeding phase.

Progesterone was continued in the same dosage until the fifth day of bleeding, at which time curettage was done. Microscopic section of curettage material showed evidence of retention of the secretory endometrium as in the previous case (Fig. 18).

**EXPERIMENTAL CASE 3.**—V. M., aged 30 years, para 0, presented no gynecologic complaints. Menses were regular, with a twenty-eight-day cycle. Last menstrual period had been January 26; expected next menses was about February 24. Beginning on February 20 (twenty-sixth day of cycle) patient was given 20 mg. of progesterone daily. This was continued until the onset of bleeding which was delayed until March 3 (thirty-seventh day of cycle). Progesterone was then discontinued. Curettage was carried out on the fifth day of bleeding. Sections showed normal regeneration phase endometrium (Fig. 19).

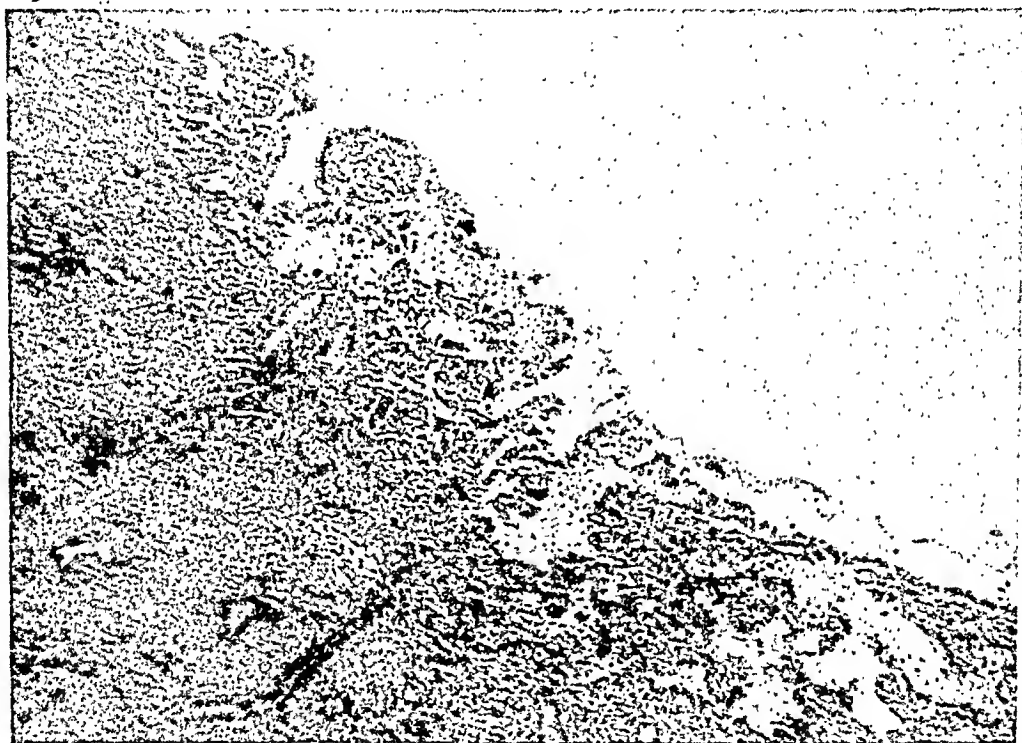


Fig. 21.—Same case as Fig. 20. Endometrium obtained on fifth day of bleeding after continuation of progesterone administration into bleeding phase. Note delay in shedding and regeneration.

**EXPERIMENTAL CASE 4.**—E. D., aged 36 years, para 0, presented no gynecologic complaints. Menses occurred every twenty-eight to thirty days. Her last menstrual period had been February 5, and expected next menses about March 5. Twenty milligrams of progesterone were administered daily beginning on March 2 (twenty-sixth day of cycle). Dose decreased to 10 mg. daily beginning on thirty-third day of cycle when bleeding had failed to occur. This dosage was continued daily until four days after bleeding had begun (thirty-eighth day of cycle). Endometrial biopsy was taken on thirty-sixth day of the cycle. This showed a markedly excessive secretory change in the endometrium (Fig. 20). Curettage was done on the fifth day of bleeding. Section showed beginning evidence of regeneration of the surface and less retention of secretory endometrium than in case 1 (Fig. 21). Note that the dose of progesterone in this case was only 10 mg. daily, as compared with 30 mg. used in case 1.



If the hypothesis of prolonged progesterone effect be correct, it should be possible to reproduce the disease in the normal patient by administering progesterone during the bleeding phase of the cycle. We have attempted to do this with interesting results.

EXPERIMENTAL CASE 1.—V. W., aged 16 years, para 0, presented no gynecologic complaints. Menses were regular every thirty days with a four- to five-day flow. Recent periods of bleeding before administration of hormone were as follows: February 22; March 23; April 18. As soon as bleeding was noted on April 18, injections of progesterone were started. Thirty milligrams of progesterone in oil were administered daily for the next six days, during which time bleeding continued in small amounts. On the sixth day after the onset of bleeding, curettage was carried out. A large amount of endometrium was obtained, a typical section of which is shown in Fig. 17. The surface epithelium is intact, the glands show marked secretory change, and the stroma is overdeveloped. This picture is similar to that seen in the endometrium removed from our clinical case 1 (Fig. 2).



FIG. 20.—Experimental case 4. Endometrial biopsy taken on thirty-sixth day of cycle after administration of progesterone beginning on twenty-sixth day of cycle.

EXPERIMENTAL CASE 2.—R. M., aged 23 years, para 0. No gynecologic complaints. Menses occurred every twenty-six to twenty-eight days. Beginning on the twenty-fourth day of the cycle the patient was given 10 mg. of progesterone daily. Bleeding began on the thirty-first day of the cycle.

5. Diagnostic curettage must be done during the bleeding phase of the cycle in order to make the diagnosis.

6. The microscopic picture characteristic of the disease can be reproduced in the endometrium of the normal female by the injection of progesterone during the bleeding phase of the cycle.

7. Administration of progesterone during the latter part of the cycle will delay the onset of menstrual bleeding.

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These studies would seem to indicate that at least the microscopic picture which we recognize as characteristic of irregular shedding of the endometrium can be reproduced in the normal patient by administration of proper doses of progesterone during appropriate phases of the cycle. Apparently progesterone must be administered during the bleeding phase in order for the secretory endometrium to be retained. Administration of progesterone in dosage of at least 20 mg. daily during the last portion of the cycle will delay the onset of menstruation. However, there appears to be a critical level above which bleeding can be prevented indefinitely from occurring. In our cases this seemed to require a dosage of between 20 and 30 mg. of progesterone daily. A dosage of 10 mg. daily did not prevent menstruation from occurring, but the expected period was delayed in its onset. The endometrium will be shed in the usual period of time unless progesterone is continued in a dosage of at least 20 mg. daily during the bleeding phase. In none of the experimental cases was bleeding profuse when it did occur. Whether or not bleeding would have been prolonged will have to be determined by future studies in which the patient is allowed to bleed without curettage having been performed.

### Treatment

At the present time no recommendation as to treatment can be made. Previous authors have stressed the fact that curettage alone acts as a therapeutic as well as a diagnostic procedure. Our experience has not been so fortunate. Reference has been made to three cases finally treated by hysterectomy after repeated curettage had failed to be of therapeutic value. Administration of estrogenic substance during the bleeding phase might be expected to speed up the process of regeneration. This type of therapy was tried out on three of our patients without noticeable effect either on the amount or the duration of the bleeding. One patient who was ultimately subjected to hysterectomy felt that the estrogen therapy made the bleeding more profuse. We feel, however, that this form of therapy has not received an adequate test and should receive further trial. In the menopausal group, sterilization by irradiation is the treatment of choice.

### Summary and Conclusions

1. Cyclical menorrhagia is frequently caused by irregular shedding of the endometrium.

2. Irregular shedding of the endometrium is a clinical and pathologic syndrome characterized by a typical pathologic picture, the outstanding feature of which is prolongation of shedding of the endometrium which has undergone progesterone stimulation.

3. The diagnosis depends upon correlation of the endometrial pattern with the menstrual history. Knowledge of the menstrual history is essential for a histologic diagnosis.

4. During the nonbleeding phase of the cycle the endometrium may be normal.

### Methods and Materials

Previous clinical experience had shown that larger doses of commercial preparations produced rather severe local reactions in some patients. Furthermore, the contemplated dose could not be given in a reasonable volume if the regular trade preparations were used. Chorionic gonadotrophin (Antuitrin-S) was generously furnished by Parke, Davis, & Company as a dry powder. It was dissolved in a phosphate buffer (pH 7.4) so that each ml. contained 5,000 I.U., and the solution was sterilized by passing through a Jena filter. No preservative was added to these solutions. Cheek assays on immature rats indicated these solutions were up to expected potency. Women with normal menstrual function were selected for this study, and the effects of treatment were determined by obtaining endometrial biopsies once or twice a week. The urine was collected and processed for pregnanediol by the method of Astwood and Jones.<sup>6</sup> In several patients scheduled for elective surgery it was possible to observe or obtain an ovary at the time of laparotomy. The injection of these large doses of chorionic hormone did not produce any systemic or local effects of significance. There was never anything more than a mild local reaction which suggests that the preservative used in commercial preparations may be a factor in some of the more extensive local reactions seen previously.

### Observations

Two subjects (W. P. and N. W.) received 20,000 I.U. daily beginning in the late secretory phase. The menstrual period was delayed by nineteen days and twelve days, respectively, and during this time decidual changes were present in the endometrium as determined by biopsy (Fig. 1). Bleeding occurred during and despite continued treatment. The subsequent cycles of these patients were normal. The urine of these patients obtained during treatment produced a positive Aschheim-Zondek test.

In the third subject (L. A.) chorionic hormone, 10,000 I.U. daily, was given as indicated, and essentially the same effects were observed. This experiment was terminated by laparotomy on the fourteenth day after starting treatment. Endometrial biopsies had shown a definite decidual reaction, and at laparotomy a well-formed and apparently active corpus luteum was found. This was present twelve days after the expected menses. This corpus luteum was associated with a delayed menstrual period, with a persistence of pregnanediol excretion ten days beyond the usual life span of a corpus luteum spurium, and with a decidual reaction in the endometrium (Figs. 1, and 4 to 7). Urine obtained from this subject on the fourth day of treatment gave a positive Aschheim-Zondek test.

Since doses of 20,000 I.U. and 10,000 I.U. per day had a definite luteotrophic effect and had produced a pseudopregnancy, it was of interest to determine what would be a minimal effective dose. Daily doses of 5,000 I.U. and 2,500 I.U. were tried, and the results are shown in Fig. 1. In the subject (B. L.) who received 5,000 I.U., the duration of the pseudopregnancy was shorter, and the amount of pregnanediol in the urine was smaller. Menstruation started on the thirteenth day of treatment, and at laparotomy the following day the left ovary was removed. It contained a large well-formed corpus luteum and many normal immature follicles. Doses of 2,500 I.U. delayed the onset of menstruation not more than two or three days. In both cases it started after ten days of treatment, and the predecidual changes were no greater than those seen in normal cycles. The quantity of pregnanediol recovered from the urine of one of these patients (M. B.) was larger than from any other patient in this study, and it is peculiar that she started to bleed while the pregnanediol values were still being

## A STUDY OF THE PHYSIOLOGIC ACTION OF HUMAN CHORIONIC HORMONE\*

### The Production of Pseudopregnancy in Women by Chorionic Hormone

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IN 1927 the urine of pregnant women was shown to contain a substance which was gonadotrophic in infantile mice. This material was extracted and made available for clinical use a few years later, and is generally known as chorionic gonadotrophin. This material has been extensively studied in the laboratory, and the literature is replete with reports of the effect of chorionic hormone on experimental animals. The results of using this hormone in women are inconclusive and contradictory. Most of the clinical reports deal with cases of an assumed physiologic derangement treated according to a hypothesis developed in the laboratory and transferred to patients. Both the correctness of the diagnosis and the validity of the transfer are often in doubt. Because of this we decided to study the effect of chorionic hormone in *normal* women. This communication presents a series of observations in which large doses of chorionic hormone induced a pseudopregnancy in women (persistence of the corpus luteum, decidual changes in the endometrium, prolonged excretion of pregnanediol, and positive Aschheim-Zondek tests on the urine).

### Historical

In a review of the literature up to 1939, Engle<sup>1</sup> concluded that in monkeys and women, treatment with chorionic hormone produced follicular degeneration but the effects on the corpus luteum were equivocal. Hamblen<sup>2</sup> treated 37 cases of functional bleeding and in no case was there any evidence of induced luteal function. Browne and Venning<sup>3</sup> reported that when treatment was started during the luteal phase of the normal cycle there was an increased and prolonged excretion of pregnanediol, and the onset of the next menstrual period was delayed. In 1940 the authors<sup>4</sup> used doses comparable to those employed by Browne and Venning, but did not observe any alteration in menstrual rhythm or in the cyclic changes in the endometrium during the period of treatment. In some patients there was an amenorrhea of two or three months' duration after cessation of treatment, and the endometrium became atrophic during this interval. In no case was there any evidence of induced or prolonged luteal function. The physiologic action on the corpus luteum of the monkey was investigated by Hisaw.<sup>5</sup> He found that relatively large doses of pregnancy hormone would prolong the functional phase of the corpus luteum as much as fourteen or fifteen days. Cognizant of the fact that the pregnant woman excretes much larger quantities of chorionic gonadotrophin than does the monkey and of our previous negative findings with doses of 500 R.U. per day, it was decided that the effect of large doses should be determined in normal women. Urinary excretion values of pregnancy indicated that doses of 10,000 to 20,000 I.U. might approximate the amounts normally present in the first week or two of pregnancy.

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days). In three cases the cycles were of normal length, and the secretory changes in the endometrium were normal in onset and duration (D. A., M. J. 1, and K. B.). There was no secretory change in the endometrium until after eight days of treatment in two of these patients, so there is no indication that ovulation or the onset of luteal function was hastened. The pregnanediol excretion was of normal duration in L. A., but none was ever recovered from the urine of K. B. except for a trace the day before the onset of bleeding. In only one subject was there a delay in the onset of menstruation and a decidual change which indicated that the therapy had influenced the ovarian cycle (W. P.). These observations indicate that the chorionic hormone may have little or no effect on the maturing ovarian follicle.

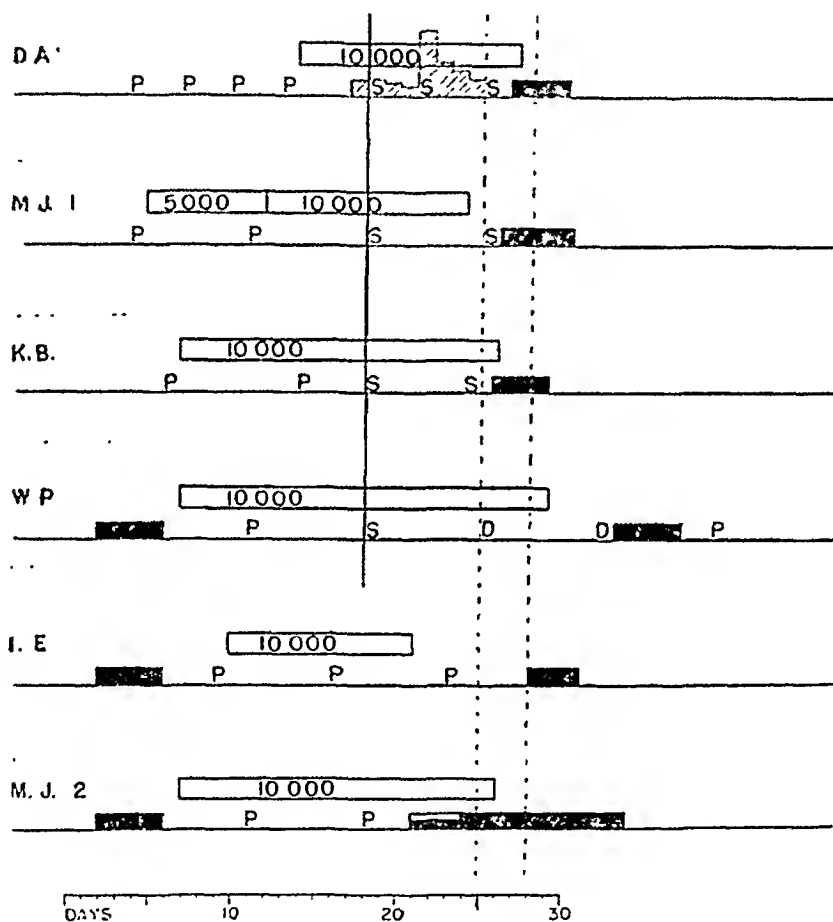


Fig. 2.—Graphic representation of the observations on five subjects in whom treatment was started in the preovulatory (follicular) phase of the cycle. The menstrual periods, biopsies, and treatment are represented in the same manner as in Fig. 1. M. J. 1 and M. J. 2 is the same patient treated at different times.

Two subjects were treated very late in the secretory phase. The initial injection of chorionic gonadotrophin was given within twenty-four hours of the onset of bleeding (N. W. and M. W., Fig. 3). No effect was obtained, so apparently the hormone is unable to revive an involuting corpus luteum.

Chorionic hormone was also given to a castrate (N. D., Fig. 3). This patient had been treated with estrogen and progesterone until the endometrium had developed a secretory pattern. Then injections of chorionic hormone, 10,000 I.U. daily, were given, but had no effect: the endometrium was not converted to a decidua, and the patient menstruated after cessation of the ovarian hormone therapy. This would indicate that the action of the chorionic hormone is through the corpus luteum and not directly on a secretory endometrium.

maintained. It was not possible to obtain urine for pregnanediol from the other patient receiving this dose. From these observations it appears that at least 5,000 I.U. daily is necessary to produce a definite pseudopregnancy.

It was of interest to study the urinary excretion of chorionic hormone to determine the renal threshold for this substance. After four to five days of treatment the urine was collected and tested by injection of 3 c.c. into immature female rats. The urine of patients receiving 10,000 and 20,000 I.U. daily produced positive Aschheim-Zondek reactions, but the urine of the patients receiving 5,000 and 2,500 I.U. daily was negative. This indicates that the developing trophoblast must produce over 5,000 I.U. daily before the Aschheim-Zondek test becomes positive. Thus it is possible for an early pregnancy to maintain the corpus luteum with an amount of chorionic hormone insufficient to give a positive Aschheim-Zondek test. This may explain the negative Aschheim-Zondek tests in the first few days of pregnancy.

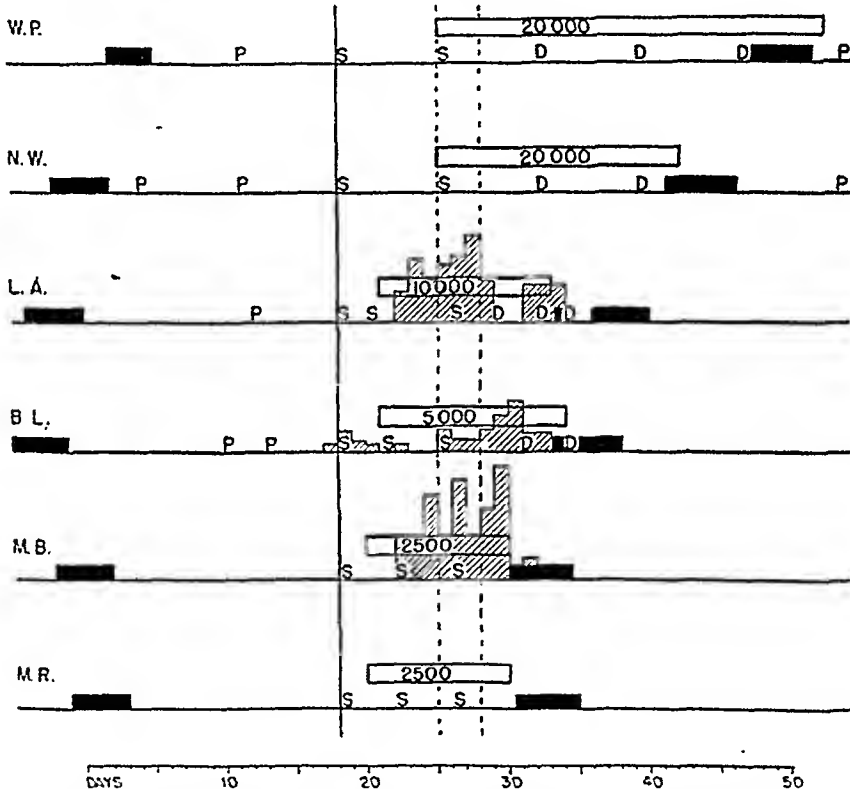


Fig. 1.—Graphic representation of the observations on six subjects in whom treatment was started in the premenstrual (luteal) phase of the cycle. The black bars represent menstruation. The letters represent endometrial biopsies, P for proliferative, S for secretory, D for decidual reaction, and R for resting. The vertical line indicates the date of the first secretory biopsy, and the vertical broken lines the approximate interval of expected menstruation. The open bars indicate the duration of treatment, and the numbers denote the dosage of chorionic hormone in I.U. per day. The shaded bars represent the excretion of pregnanediol in mg. per day.

Having demonstrated that chorionic gonadotrophin would prolong the functional life of the corpus luteum, it was of interest to determine whether it would have any effect in the follicular phase of the cycle. Treatment was started in the preovulatory interval in five subjects (Fig. 2), one of them being treated twice (M. J. 1 and M. J. 2). Daily doses of 10,000 I.U. were employed, since this procedure had been found effective when started in the luteal phase of the cycle. In two instances the endometrial biopsies failed to reveal any evidence of a secretory change (I. E. and M. J. 2). In the case of M. J. 2 the interval was short (nineteen days) and the subsequent bleeding was prolonged (thirteen

### Discussion

These observations show that chorionic gonadotrophin will prolong the functional activity of a corpus luteum, and thereby give rise to a condition of pseudopregnancy. Also, that chorionic hormone failed to influence the developing follicle, failed to revive a regressing corpus luteum, or to affect the secretory endometrium in a castrate. Since the action of this placental hormone was limited to the maintenance of a pre-existing functional corpus luteum, it appears to be a luteotropic agent.

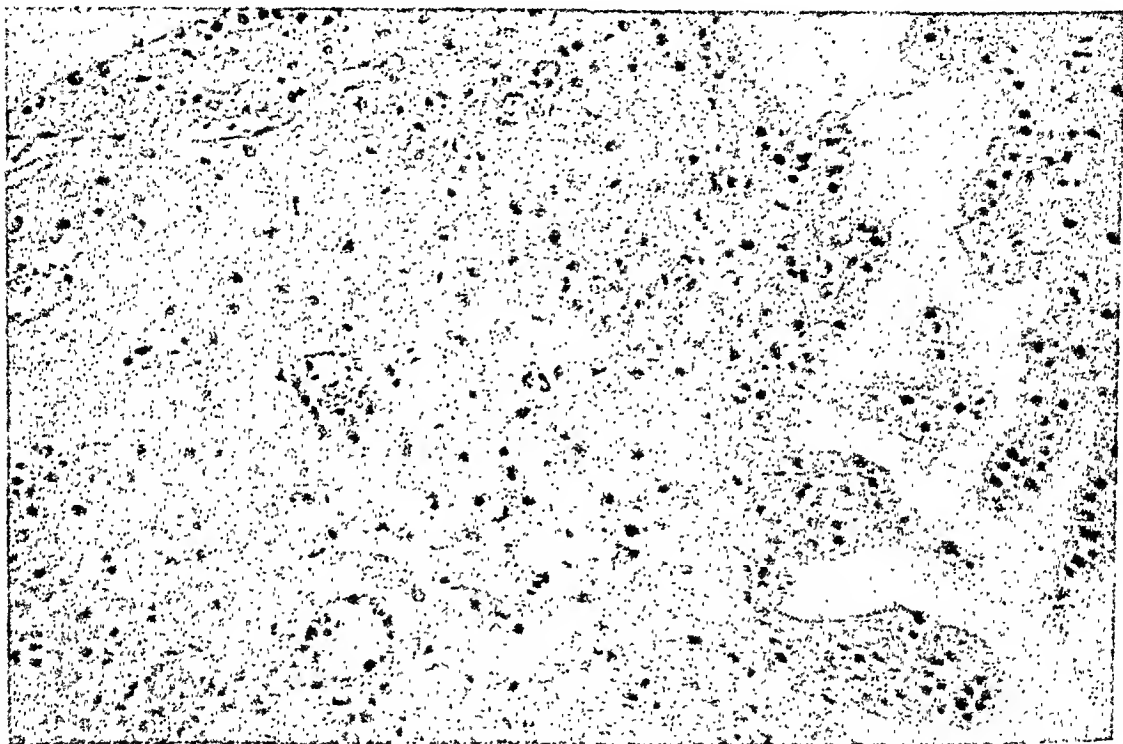


Fig. 5.—L. A. Endometrial biopsy, May 16, on ninth day of treatment, 10,000 I. U. daily. Secretory activity in glands and decidual change in the stroma.

On this evidence it seems that the chorionic gonadotrophin is a hormone that is responsible for the early development of the corpus luteum of pregnancy. This is the first objective study of which we are aware that demonstrates the probable physiologic action of this placental hormone in women. The prolonged excretion of pregnanediol confirms the early report of Browne and Venning, but we cannot confirm their statement that, when treatment is started early in the cycle, it hastens the onset of luteal function.

It is of interest to speculate why human chorionic hormone has not duplicated these results in the experimental animal. In the evolutionary development of the higher forms, some mechanism was necessary to retain the embryo in a place of protection. As one ponders on the transfer from the oviparous to the ovoviviparous to the viviparous mechanisms, it is obvious that some system must be developed which would prolong the time that the embryo would be retained within the maternal system. The literature lists a variety of such mechanisms

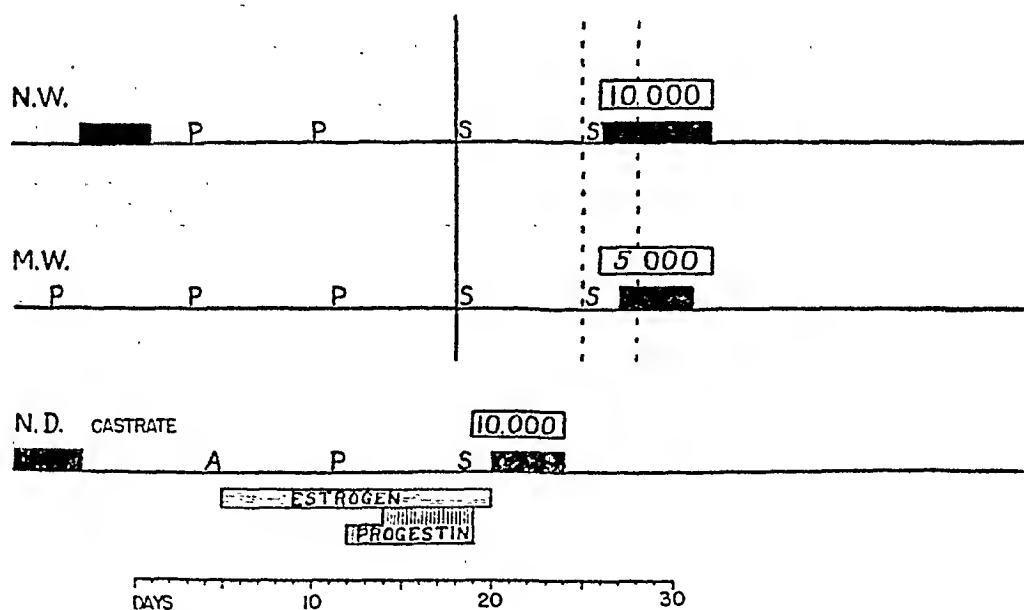


Fig. 3.—Graphic representation of the observations on two patients in whom treatment was started within twenty-four hours of the onset of menstruation and on a castrate patient. The endometrium of N. D. had been developed by administering an aqueous suspension of estrogen (Lakeside) in eight doses of 4 mg. each on alternate days, and progesterone (Lipo-Lutin) in doses of 20 mg. for two days, and then 40 mg. per day for five days.

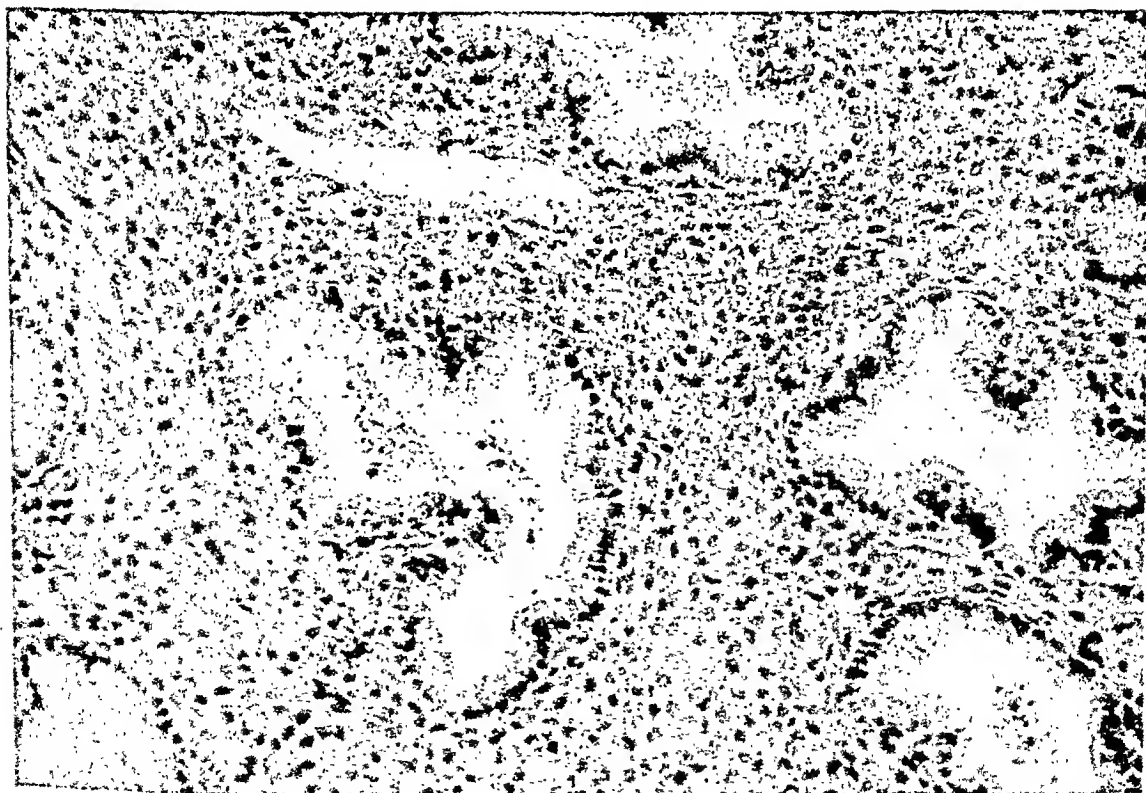


Fig. 4.—L. A. Endometrial biopsy, May 7, on the twenty-sixth day of cycle. Secretory phase. Treatment started the following day.



developed by the different species. The mammalian group has developed the highly specialized placenta which takes over an endocrine function. The placental tissue in mares, monkeys, and women produces a substance which gives an Aschheim-Zondek reaction. The placenta of most other species does not produce this type of gonadotrophic agent. However, the rat placenta has been shown to contain a substance capable of prolonging the function of the corpus luteum in the adult rat.<sup>7</sup> This luteotrophic extract was also effective in maintaining the corpus luteum after hypophysectomy, but it was devoid of any follicle-stimulating or luteinizing action in the infantile rat.

The hormone of pregnant mare's serum is peculiar in that it is not excreted in the urine, and, when tested in the infantile rat, it produces extensive follicular stimulation. Human placental hormone is excreted in the urine and it produces marked luteinization of the infantile rat ovary. The chorionic hormone of human pregnancy urine should be recognized as a primate pregnancy hormone since it does not exist in any of the subprimate animals. Thus, it appears that horse chorionic hormone in the horse, rat chorionic hormone in the rat, and human chorionic hormone in the human all have a similar luteotrophic effect which may be species specific, but, when these placental substances are injected into foreign species, they may not exhibit a typical luteotrophic action.

The chorionic hormone, being a pregnancy hormone, would logically be used as replacement therapy in abnormalities of early pregnancy. On this basis, it might be indicated in preventing abortion in patients if the threatened or habitual abortion was due to a failure of the trophoblast to produce adequate amounts of luteotrophin. It might also be indicated in certain sterility problems where luteal function may be inadequate for implantation. Aside from pregnancy, it might be of benefit in certain types of menorrhagia due to defective luteal function. Since the luteotrophic action of the chorionic hormone is the only objectively demonstrable action in women, it would not be indicated for the treatment of amenorrhea or anovulatory sterility.

While the doses of chorionic hormone used in this study seem large in terms of previous clinical practice, it should be recalled that the normal amount of chorionic hormone in the urine of early pregnancy often exceeds 200,000 I.U. per day. Common clinical dosage has been based on commercial costs and tolerated doses rather than physiologic requirements.

### Summary

1. Human chorionic hormone is luteotrophic in women and will induce a pseudopregnant condition, as evidenced by a prolongation of the functional life of the corpus luteum, the development of a decidua, and the prolonged excretion of pregnanediol.

2. The effective dose of chorionic hormone seems to be 5,000 I.U. to 10,000 I.U. daily. These doses may be given without untoward reactions.

3. Until objective evidence of other gonadotrophic action in women is obtained, the use of human chorionic hormone should be directed toward the maintenance or augmentation of luteal function.



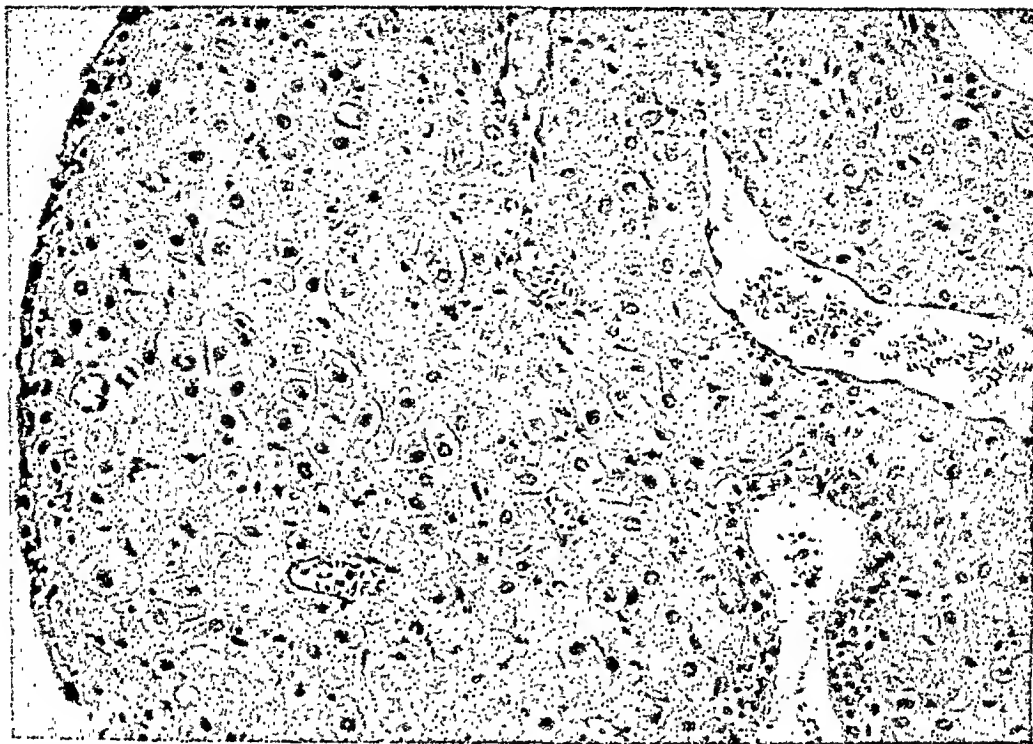


Fig. 6.—L. A. Endometrial biopsy, May 21, on day of laparotomy. Fourteenth day after starting treatment. Menstrual period delayed twelve days. Marked decidual change and increased vascularity.



Fig. 7.—L. A. Ovary and tube removed May 21. Ovary cut open to show the large cystic corpus luteum. Treatment started fourteen days previously, menstrual period delayed twelve days.

## COMBINED EVIPAL AND SCOPOLAMINE ANALGESIA AND CYCLOPROPANE ANESTHESIA IN OBSTETRICS\*

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THE demand of the obstetric patient for the relief of pain during labor has become almost universal. The desire for alleviation of pain during parturition is as old as the beginning of the human race. Much progress has been afforded the patient during the last thirty-five years. But in her intense desire to avoid pain the patient picks up from lay press, motion pictures, and radio many misconceptions. It seems a pity that medical research is not more careful in reporting tentative findings, and that lay sources are not more responsible in interpreting these articles to the public.

I am certain we all agree that anesthesia can usually be produced by introducing an anesthetic agent into either the caudal or spinal canal. However, physicians know that before these methods can safely be publicized to the laity there must necessarily be a great deal of laborious observation recorded on a large series of patients. Such careful testing should certainly precede enthusiastic claims for any anesthetic before it is publicized to the laity. We must bear in mind that no anesthetic agent, whether it be given by inhalation or injection either intravenously, rectally, or by means of the caudal or spinal canal, can be administered without increasing to some degree the percentage of maternal and fetal mortality. It is the duty of the research worker through meticulous animal and clinical experimentation scrupulously to weigh his findings before passing them on to the clinician. If this careful scientific approach is used in studying the actions of analgesics and anesthetics, the obstetric patient will be guided by her physician, who will utilize the safest method appropriate to her individual case; and she will not demand some particular method of pain alleviation suggested by an ill-informed lay person.

In 1941, with Bohlender,<sup>1</sup> the writer described the amnesic action of evipal soluble given rectally and scopolamine hydrobromide given hypodermically in a series of 53 cases studied at the University Hospital. Actual anesthesia at time of delivery was accomplished by the inhalation of ether. Our conclusions stated that evipal soluble given rectally was a safe and effective analgesic; that its amnesic effect was greatly enhanced by the use of scopolamine hydrobromide given hypodermically; and that this method of analgesia was sufficiently satisfactory to merit further study in a larger series of cases. Since the publication of this paper, very few articles describing the use of these drugs in obstetrics have appeared in the literature. Thoms and Taylor<sup>2</sup> reported favorably upon their use in 110 unselected obstetric patients. They substantiated our conclusions and stated their belief that evipal soluble and scopolamine given

\*Presented before the Central Association of Obstetrics and Gynecology, Fourteenth Annual Meeting, Chicago, Ill., Sept. 19 to 21, 1946.

The authors express their appreciation to Doctor J. R. Porter of the Department of Bacteriology for his assistance and cooperation in the preparation of the Jena filters.

Through the courtesy and cooperation of Doctor A. Soucek patients at the Mount Pleasant State Hospital were made available for these observations.

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part caused perineal signs denoting imminent delivery, and then only after the patient had been transported from the labor to the delivery room.

### Effect of Drugs Upon the Mother

The analgesic and amnesic effect of the combination of evipal and scopolamine was most gratifying.

The rapidity of action is one of the most startling qualities of evipal given rectally. Some patients became drowsy and sleepy within three minutes; others, not before ten minutes; the average time was five minutes before the patient was asleep. Ordinarily the patient slept soundly between uterine contractions, but was aroused while having a pain, only to lapse into unconsciousness after its completion. After labor has actually begun and the cervix effaced and dilated sufficiently, the drugs may be given with benefit any time during the course of labor, but the earlier they are given, especially in multiparas, the more complete the sedation.

It is necessary for a nurse to be in constant attendance upon the patient while in labor. Only 5 per cent of patients were difficult to manage while having pain. These thrashed about the bed, wanted to sit up, get out of bed, et cetera. All of these patients were unaware of their actions, and reported total amnesia regarding their labor.

Complete analgesia and amnesia during labor were experienced by 93 per cent of the patients studied. Upon being questioned, they all volunteered that they remembered nothing about their labor after rectal instillation of evipal. The average patient slept from one and one-half to two hours after her delivery. Upon waking, the majority of mothers inquired when they might expect the birth of their baby. Seven per cent of the patients received only fair sedation, and some remembered almost everything about their labor until the time of administration of cyclopropane, while others had a hazy recollection of pain and discomfort up to the time of anesthesia. A review of their charts showed that the majority of these patients had been given castor oil for induction of labor. Since then, castor oil has been eliminated in the routine of induction of labor, and no failure to produce good amnesia has been encountered.

No maternal deaths were reported.

The length of labor was not increased, and textbook figures for the duration of labor were actually shortened, since the drugs do not diminish either the intensity or duration of the uterine contractions once the patient is in actual labor. However, if sedation is given too early, i.e., before pains are well established and before effacement and dilatation of the cervix have begun, the patient may go to sleep and labor pains stop entirely. In primiparas, the average length of labor was eleven hours and thirty-nine minutes; in the multiparas, nine hours and forty-one minutes.

Although evipal is reported to be detoxified rapidly in the liver<sup>7</sup> there is no clinical evidence to cause hesitation in using this drug in pre-eclampsia. Twenty cases of mild and severe pre-eclampsia were encountered in this series in which evipal and scopolamine were used as sedation. One primipara who became mildly toxic during her last week of pregnancy delivered normally, but developed postpartum convulsions within two hours following delivery. Recovery was prompt after dehydration therapy was instituted.

### Administration of Cyclopropane

Cyclopropane gas ( $C_3H_6$ ) was first used as an anesthetic in surgery by Waters<sup>8</sup> in 1934. A colorless, nonirritating gas with a sweet odor and taste, it has the most powerful anesthetic potency of any of the gaseous anesthetics,

in proper sequence and with suitable selection had satisfactory and safe results. The ease of administration and effectiveness of amnesia of these drugs have been proved by various other workers, as Gwathmey,<sup>3</sup> Siegler and Beris,<sup>4</sup> McNellis,<sup>5</sup> and E. Petersen.<sup>6</sup>

In order to present a larger series of cases, 700 private obstetric cases at the Immanuel Hospital were studied, wherein evipal soluble was used rectally and scopolamine hydrobromide hypodermically, combined with cyclopropane anesthesia. These cases were delivered during the interval of January, 1941, to June, 1946. The major portion of this time represents the recent war period when the ranks of the nursing and intern staffs were sorely depleted by mobilization of medical personnel into the Armed Forces. The Immanuel Hospital is a general hospital of 175 beds, with the obstetric department housed on one floor segregated from the rest of the hospital. The average number of cases delivered by all physicians per year was 850. These were cared for by the attending staff, the majority of whom were certified obstetricians. No resident physician was in attendance; the intern staff was augmented by senior medical students. Thus, it is plain to see that if analgesia was to be used, it must have a wide margin of safety and be easily administered by nurses who could sit with patients throughout their labor. The cyclopropane was administered by qualified registered nurse anesthetists.

### Administration and Dosage of Evipal Soluble and Scopolamine Hydrobromide

A change in dosage of evipal soluble from that of the first series of cases was found to be effective. Whereas the average dosage of evipal at first was 1 Gm., in this study the dosage was increased to an average of  $1\frac{1}{2}$  Gm. given rectally. The technique of administration remained simple. All patients upon being admitted to the obstetric pavilion were given a cleansing enema. Thus it was not necessary to repeat this procedure before administration of the drug.

The criteria used in determining the proper time for the administration of analgesia were: (1) when it was definitely ascertained that the patient was in true labor; (2) when she began to complain of pain and ask for relief; and (3) after the cervix showed effacement and three or more centimeters of dilation. Evipal soluble crystals ( $1\frac{1}{2}$  Gm.) were dissolved in 60 c.c. of tap water. The patient was instructed to lie on her left side, and an ordinary soft rubber catheter was inserted, usually 4 to 5 inches into the rectum so that the tip of the catheter would remain above the level of the presenting part of the fetus, so the flow of the solution would not be inhibited. The evipal mixture was allowed to flow through a funnel into the catheter by gravity. The buttocks were pressed together for about ten minutes, especially during the time the patient was experiencing pain. A digital rectal examination was not done for at least thirty minutes after withdrawal of the catheter.

Scopolamine hydrobromide ( $\frac{1}{150}$  grain) was given hypodermically at about the same time as the rectal instillation of evipal. An additional hypodermic injection of scopolamine hydrobromide ( $\frac{1}{200}$  grain) was given one hour after the first injection or later during labor, if considered necessary for good amnesia. In only 25 per cent of cases was this considered necessary. In only one case in this series was it necessary to repeat the administration of evipal. Cyclopropane gas, given by inhalation for anesthesia, was not employed until the presenting

This list shows clearly that the analgesia and anesthesia given during labor in no way caused the small number of stillbirths reported.

No actual fetal asphyxia was encountered. The majority of all babies cried spontaneously a few moments after being born. Fifty babies required resuscitation. The majority of these cried shortly after delivery, but did not breathe well subsequently. After the usual procedure of clearing the air passage of mucus and placing the baby in a respirator for a few moments, all regained normal respiratory function directly and gave no further concern. Although barbiturates are known to pass through the placenta to the fetal circulation, there seemed to be no evidence of harm to the fetus when evipal was given late in labor. Several patients did not receive their sedation until within one hour of delivery; one multipara only thirty-two minutes before delivery.

### Cervical Laceration

As a customary routine procedure following the third stage of labor, the cervix of each patient was examined carefully for possible laceration. When lacerations were found with frank bleeding or enough extensiveness to delay postpartum healing, all such tears were immediately sutured and this fact recorded on the patient's labor record. The total number of such lacerations in this series was 31. One secundogravida, after a long hard labor with complete effacement of the cervix and with no dilatation greater than 3 cm., required Dührssen's incision of the cervix to facilitate delivery.

### Instrumental Deliveries

Table I represents a summary of instrumental aids used in delivery of 705 babies.

TABLE I

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1. Low (perineal) forceps—312—44%
a. Primiparas—212
b. Multiparas—100
2. Midpelvic application—47—6%
a. Primiparas—22
Kielland rotation for occiput posterior—10
Kielland rotation for occiput transverse—12
b. Multiparas—25
Kielland rotation for occiput posterior—11
Kielland rotation for occiput transverse—11
Tucker-McLean rotation for occiput transverse—3
3. Breech delivery—31
Piper forceps for aftercoming head—5

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In the primigravida there was no hesitation in applying forceps to the head of the child prophylactically when the presenting part was on the perineum. This was generally done after performing an episiotomy, a maneuver necessary in less than half the number of multiparas. The use of perineal forceps definitely shortens labor and also acts as a protective measure by diminishing trauma to the fetal skull. There is no evidence of increase in the incidence of midforceps application in this series.

### Discussion

The purpose of this report is to present a statistical study of the amnesic action of a little publicized barbiturate combined with scopolamine in a large enough series so that certain clinical conclusions may be drawn. Inasmuch as cyclopropane has proved to be an effective anesthetic when used with sedatives

according to Lull and Hingson.<sup>9</sup> It is highly inflammable. In 3 to 5 per cent concentration it will produce analgesia; 6 to 8 per cent will produce unconsciousness; 20 to 25 per cent will maintain surgical anesthesia. This gas has two very important properties which are highly acceptable for obstetric deliveries, e.g., rapidity of action, and no effect of decreased uterine contractions during light anesthesia. The high percentage of oxygen used in combination with cyclopropane is also highly favorable to both mother and child.

As previously stated, cyclopropane is not administered until the patient has been transported to the delivery room and birth of the child is imminent. The actual administration of cyclopropane is entrusted to one of three qualified nurse anesthetists, who are alternately on call for obstetric anesthesia. The gas is given through a closed system machine. The face piece is secured over the nose and mouth, and the patient is given a few inhalations of 100 per cent oxygen before this concentration is diluted with 50 per cent cyclopropane. As unconsciousness ensues, the mixture may be reduced to 10 to 15 per cent cyclopropane and 85 per cent oxygen. The depth of anesthesia is markedly increased during labor pains. With effective evipal-scopolamine analgesia the mixture of cyclopropane may be reduced to as little as 3 to 5 per cent. The proportion of cyclopropane-oxygen is maintained until after the birth of the baby, whereupon the oxygen content is again raised until the umbilical cord is severed. If repair of an episiotomy or laceration is necessary, the concentration of cyclopropane may be raised to 15 to 20 per cent, to maintain surgical anesthesia.

Because cyclopropane is highly inflammable and explosive, certain precautions must be insisted upon in its administration. Every precaution against the production of static sparks was used. In the delivery room all electric lights were turned on before the gas was used; no rubber-soled shoes were worn; and no smoking was allowed near the delivery rooms. Cyclopropane was curtailed during electric storms. The patient and anesthetist were meticulously grounded to prevent disaster. As a further safety measure, helium has been introduced to act as a buffer against explosion by reducing the oxygen ratio. Thomas<sup>10</sup> has suggested the employment of inert helium in the initial flow of anesthesia to the patient; he recommends 1,000 c.c. of helium, 500 c.c. of cyclopropane, and 500 c.c. of oxygen. After three minutes the helium is reduced to a flow of 150 c.c. Oxygen is carried at the metabolic need of the patient, usually from 300 to 500 c.c. and cyclopropane allowed to flow at the rate of 50 to 200 c.c. according to the requirement for anesthesia. In our series of cases, no explosions were encountered.

### Effect Upon the Baby

In this statistical study all cases which required elective cesarean section from whatever cause were excluded. The total number of babies delivered was 705, including five sets of twins; 674 presented by the vertex and of these 602 were occiput anterior; 50 were persistent occiput posterior; 22 were transverse arrests. The number of breeches was 31: complete breeches, 24; single or double footling, 7. The number of stillbirths was 4, the causes of which were found to be the following:

1. Full-term infant born with a meningocele.
2. Seven-month gestation complicated by placenta previa marginalis.
3. Missed labor—near full term—no fetal heart or movements three weeks prior to delivery.
4. Double footling; membranes ruptured at home and nonpulsating umbilical cord presenting at the vulva upon hospital admission.

Five per cent of our patients became difficult to manage under evipal and scopolamine. This is a strikingly smaller proportion than is reported with use of other barbiturates and scopolamine.

The number of instrumental deliveries will be increased whenever sedation is employed. Inhalation anesthesia usually increases the necessity for the application of forceps; especially true in the use of ether, due to the abolition of uterine contractions. Cyclopropane has the advantage of not decreasing uterine contractions materially; thus it reduces the use of forceps to the outlet variety when the head is actually on the perineum. There is no contraindication in using evipal-scopolamine combination in multiple pregnancies, forceps rotation of occiput posterior and transverse arrests, or in breech deliveries.

Cyclopropane should not be used in doing internal podalic versions. The uterine muscle cannot be relaxed sufficiently to permit accomplishing this obstetric operation safely.

On three occasions the progress of labor was inhibited due to the existence of Bandl's contraction ring. Adrenalin was given, and the anesthetic was changed from cyclopropane to ether. No untoward reaction was noted in using adrenalin while cyclopropane was being administered.

No evidence of cardiac irregularities was seen in any patient studied in this series.

Blood loss was not actually measured in this series, but the average loss per case could be estimated at less than 400 c.c., thus substantiating Greenhill's<sup>12</sup> observation with regard to cyclopropane. Due to the high concentration of oxygen in the anesthetic mixture the blood appears much redder than when nitrous oxide, for instance, is used, thereby giving the impression of greater blood loss.

No evidence of proctitis following rectal instillation of evipal was observed in any case in this series.

Effective sedation is considered an aid in cervical dilation, since it reduces spasticity of the cervical muscle fibers and thereby minimizes the incidence of cervical laceration. Inspection of each case in this series for cervical laceration showed a total number of 4 per cent. Because the cervix is not generally inspected following the third stage of labor, statistics concerning cervical laceration are not dependable.

### Conclusions

1. After carefully evaluating clinical data on 700 private obstetric cases, the combined amnesic and anesthetic action of evipal soluble given rectally, scopolamine hydrobromide given hypodermically, and cyclopropane administered by inhalation was found to be safe and effective.

2. Analgesia and amnesia were produced completely in 93 per cent of cases; 7 per cent experienced little or no relief of pain.

3. Four stillbirths were reported. The cause of each was ascertained, and in no instance did the agents used for the production of analgesia and anesthesia have the remotest connection with etiology of the fetal death. Less than 7 per cent of newborn babies required artificial resuscitation. All of these survived with no further trouble after resuscitation.



other than evipal, we were curious to study the combined actions of evipal, scopolamine, and cyclopropane.

The ideal, safe, flawless anesthetic has not yet been discovered. Any form of anesthesia or analgesia has its drawbacks. In obstetrics we must consider the effect of the drug upon both the mother as well as the child in utero; also the ease with which the drug is administered. These are the deciding factors as to the practicability of any form of obstetric analgesia.

The patients studied in this series represent a cross section of middle class private obstetric clientele in a midwestern locality. The heritage of most of these patients was north European stock; very few were of Latin extraction. All patients were given many months of careful prenatal care, and were told they could expect a certain amount of pain and discomfort during the early portion of their labor. They were promised no particular kind or type of anesthesia, but were assured that all possible relief would be afforded them when labor had reached the point at which sedation would not inhibit further progress, and would not be harmful to either the patient or unborn child. This method of psychologic preparation for labor thus prepared the patient to expect some discomfort in early labor; no patient was promised that labor would actually be painless. The production of a proper mental attitude by allaying fear has much to do with increasing the sedative value of any drug employed.

This combination of analgesic medication is useful in any hospital obstetric department which is sufficiently staffed to carry out the simple technique outlined in this report. It seems particularly applicable to the maternity pavilion in a general hospital where the attending physician must rely upon competent interns and nursing staff to carry out sedation under his direction, but without his constant attendance throughout the labor. Anesthesia induced by cyclopropane cannot be entrusted to a novice but only to a well-trained and qualified anesthetist. Such a person should be a full-time hospital employee and need only be in attendance for the actual delivery of the baby.

During the time these 705 cases were being studied, various combinations of other anesthetics were tried, i.e., 1 per cent novocain by pudendal block, nitrous oxide, and ether. With the latter two the uterine action was slowed prior to delivery, and greater delay in fetal respiratory action seemed evident. Several times when an anesthetist was not available, pudendal block by using 1 per cent novocain worked admirably. Its striking attribute was the ease with which the perineal floor relaxed, allowing the presenting part to be born often without a laceration or the necessity of an episiotomy. The ease and apparent safety of administration was also striking.

Irving<sup>11</sup> states that the combination of barbiturates and scopolamine would be ideal if it were not for the fact that they produce unfavorable maternal and fetal respiratory complications. No maternal respiratory complications of any variety were encountered in this series while using evipal and scopolamine. Less than 7 per cent of the babies required resuscitation. Of these, all breathed normally following artificial resuscitation and gave no further trouble. This small percentage may be attributed in part to the high ratio of oxygen carried while using cyclopropane.

## SURGICAL GERIATRIC GYNECOLOGY\*

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THE progressive trend toward the prolongation of the life span in the United States has made gynecologists aware of the increasing demand for the care of these elderly women. Hippocrates emphasized the need for special study and observation of senile changes and, in the eighteenth and nineteenth centuries, Floyer, Constatt, Seidel, Charcot, and others directed attention to the medical care of the aged.<sup>1</sup> In recent times Boas,<sup>2</sup> Thewlis,<sup>3</sup> and Kosmak<sup>4</sup> have stimulated interest in the patient past 50 years of age. Thus, the development of geriatrics has been slow, but surgical treatment of the aged has been particularly slow, as indicated by the few reports of studies of any large series of cases. Therefore, the following study merits attention, since it reviews the results of previous studies of gynecologic surgery in the aged, analyzes a statistical study of a fairly large series of patients, and attempts to further evaluate the advantages and conditions for gynecologic surgery in the aged, and possibly established operative mortality rates for these age groups in relation to life expectancy.

At the time of the American Revolution the mean length of life was 35.5 years; by 1900 it had risen to 50 years, and today it is over 64 years. The average expectation of life at birth for white females in the United States is 68.6 years.<sup>3</sup> Application of the present knowledge of medicine and hygiene should make it possible to extend the average length of life to about 75 years. Future medical discoveries may extend this by many years.

Nichols<sup>3</sup> attempts to present life expectancy according to mathematical deductions and states that nothing is more uncertain than one life; nothing is more sure than the law of averages on a million lives. The expectancy tables of the insurance companies furnish an absolute yardstick to measure, not one life, but the average of a group. At the age of 50 and in good health, one has an expectancy of 20 years. For each year one lives in good health beyond 50, one-half year is added to seventy. Thus, at 60, one could reasonably expect to reach 75; at 80, to just fall short of 85. Therefore, the life expectancy may be weighed against the mortality rate of the operation. At present, the mortality rates of gynecologic surgery in the aged woman have not been established.

In considering the aged woman (arbitrary basis, 60 years), much good may be achieved in prevention by periodic examination and by instituting proper therapy at an earlier and more desirable age when there is a greater resiliency of the body, organs, and tissues. But there are still the multitudes of old women who come for relief of a large number of gynecologic conditions rather late.

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4. The technique of administration of evipal and scopolamine is simple, and the action is especially rapid. The use of these drugs does not increase the need for additional nursing care over any other form of analgesia.

5. Cyclopropane is especially adapted for obstetrics because its anesthetic action is rapid and because its high oxygen content lessens fetal and maternal respiratory complications. It is highly inflammable and should be administered by a trained anesthetist only after all precautions have been taken to prevent explosions.

6. About 5 per cent of patients became difficult to manage while under sedation. This is an improvement over results with most barbiturate-scopolamine combinations.

7. Cervical lacerations in all cases amounted to 4 per cent, and were repaired immediately following delivery, whether actually bleeding or not. This small incidence of laceration speaks well for the relaxing effect of evipal and scopolamine upon the cervical muscle fibers.

8. There is an increase in the proportion of perineal application of forceps in vertex presentation, especially in primigravida, whenever analgesia and surgical anesthesia are used.

I wish to express my appreciation to Dr. Burnell V. Reaney for help in gathering statistics for this paper; to Doloris Broughten, R.N., Ruth Omig, R.N., and Mabel Owen, R.N., for their efficient administration of the cyclopropane used in these studies, and also for their help in preparing the data for the paragraph on the use of cyclopropane.

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TABLE II. INCIDENCE OF SIGNIFICANT MEDICAL CONDITIONS

HYPERTENSION	DIABETES	HEMIPLEGIA	ASTHMA	ARTHRITIS	PSYCHOSIS
217 (over 140 systolic) (272 recorded)	12	7	5	4	1
80%	3.8%	2.2%	1.6%	1.3%	0.3%
111 (over 170 systolic)					
40.5%					

Table II, which is a record of significant medical conditions, is probably incomplete, but the incidence of hypertension (80 per cent over 140, 40.5 per cent over 170) is common and is only of importance if associated with renal or myocardial damage. Wosika and Maher<sup>14</sup> found hypertension in 76 per cent of 97 cases of prolapse of the uterus. They suggested that prolapse of the uterus with resultant ureteral obstruction and hydronephrosis causes a decrease in the renal blood supply and hypertension. The other medical conditions in this age group require study and proper evaluation as to the patient's capabilities to tolerate anesthesia and operative procedures; this medical determination may require medical consultation.

TABLE III. CLINICAL PELVIC FINDINGS

<i>Pelvic Herniosus</i>	
Procidentia uteri with cystocele and rectocele	114
Prolapsus uteri with relaxed pelvic floor	52
Prolapsing cervical stump with cystorectocele	8
Cystorectocele	44
Urethrocystocele	12
Ulcerated neoplasms of labia	5
Carcinoma of vulva	1
Carcinoma of right Bartholin gland	1
Infiltrating carcinoma of urethra	1
Prolapsus urethrae	1
Vaginal bleeding	3
Vesicovaginal fistula	1
Neoplasm of corpus uteri (large or nodular corpus)	29
Abdominal mass	46
Ovarian cyst (by peritoneoscopy) (1 had been tapped five times a year for ascites for a year and one-half)	5
Ventral hernia	2
Cyst of vulva	1

It is of interest to note the predominance of pelvic herniosus (230) in the clinical pelvic findings (Table III). For many years this condition has been considered innocuous, and treatment was carried out only to relieve the discomfort of the patient. In addition to relieving the patient of her incapacitating condition, it is also important to keep in mind the effect of the prolapsed uterus and the pelvic hernia on the ureters and kidneys, as demonstrated by Wosika and Maher.<sup>14</sup> The remaining clinical conditions demanded treatment for the patient because of malignancy of the lesions. Occasionally, an unsuspected carcinoma of the corpus uteri was found in a prolapsed uterus, as well as other pathology such as fibroids, polyps, and adenomyosis.

Table IV on pathology reveals the high incidence of malignancy of the generative tract in this age group as well as benign neoplasms. Leucoplakia of the cervix is a lesion requiring eradication because of its neoplastic tendencies.

The operative procedures in Table V show the trend toward vaginal hysterectomy and pelvic herniorrhaphy (anterior colporrhaphy and perineorrhaphy) for pelvic herniosus in old women, rather than the Watkins' interposition, LeFort, or Manchester plastic. In view of the high incidence of neoplasms

For a long time these women have been considered beyond the time for any surgery and have been dealt with only palliatively and not satisfactorily. That this attitude is wrong and that these older women can tolerate surgery is supported by the following reports. Goldsmith<sup>5</sup> reported on the surgical care of ovarian tumors, 88 past 50 years, and 10 past 65 years, in a series of 344. Although this age group of patients are frequently more prone to have medical complications (cardiovascular, pulmonary, or renal) yet these complications were not sufficient to contraindicate surgery.

Kosmak<sup>4</sup> published his results from a questionnaire study in 1942. From Johns Hopkins Hospital, Te Linde sent the following statistics: 167, or 4.1 per cent, out of a total of 4,071 (from Jan. 1, 1940, to Jan. 1, 1942) were 60 years or over. In 112 operations of all types, 41 were well, 61 were improved, 7 unimproved, 3 died (due to coronary occlusion, pyelonephritis, and one was moribund from carcinoma of the bladder). He prefers pentothal sodium as an anesthetic. From Mayo Clinic, Mussey reported on statistics from 1939 to 1941; among 27,140 patients, gynecologic patients over 60 years numbered 2,430, including 390 breast cases; 585 operations were performed with three deaths, including one each from pulmonary embolism, glomerulonephritis with uremia, and pneumonia. There were 413 patients operated upon for rectocele, cystocele, and prolapse with over 95 per cent either completely cured or improved. The five-year survival rate for malignancies of the pelvic organs was 55 per cent. General anesthesia was usually employed, with spinal anesthesia, in a fair proportion of suitable cases. Maxwell reported from the University of California Hospital, 69 patients over 60 years in a series of 680 gynecologic patients in 1939 with no operative deaths, although many had hypertension and two were diabetics. The Bellevue Hospital report by Studdiford presented 7,971 gynecologic patients in a recent year; 154 were over 60 years of age. There were 63 operations, of which 28 were majors; there were 19 deaths in the entire series, of which 10 were claimed to be nonoperative. W. C. Danforth had 63 operations in patients between 60 and 75 years including breast cancers. He had no operative deaths. Ethylene was used in all but one patient. Kosmak felt that there need be no hesitancy in attacking gynecologic problems in older women because of the understanding of underlying factors and the developments in pre-and postoperative care and improved anesthetic procedures.

Liccione<sup>6</sup> obtained good results in 9 patients 63 to 96 years of age, with complete procidentia treated by the LeFort operations.

Newton<sup>7</sup> had eight operative deaths in 98 major surgical operations in patients over 70 years of age. In addition to the above, there were single case reports of operations in women of 80 and 102 years of age (de Filippi,<sup>8</sup> Ladwig,<sup>9</sup> Horta Barbosa,<sup>10</sup> Christitch,<sup>11</sup> Morton,<sup>12</sup> and Clark.<sup>13</sup>

### Material

The case records of 313 women, 60 to 87 years of age, were studied. (See Tables.) These patients were on the gynecologic services of Cook County (196), Michael Reese (76), and Mt. Sinai Hospitals (41).

TABLE I. AGE INCIDENCE (60-87 YEARS)

AGE 60-65	66-70	71-75	76-80	81-87
173	89	29	18	4
55.3%	28.4%	9.3%	5.8%	1.2%

TABLE VI. ANESTHESIA EMPLOYED AT OPERATION

Local (1% procaine)	100
Local and ether	3
Local and ethylene	4
Local and cyclopropane	2
Nitrous oxide	17
Nitrous oxide, oxygen and cyclopropane	1
Nitrous oxide and ether	70
Ethylene	26
Ether and ethylene	4
Ethylene and cyclopropane	4
Cyclopropane	24
Spinal	28
Sacral block	6
Continuous caudal	7
Intravenous pentothal	1

TABLE VII. POSTOPERATIVE RESULTS

	COOK COUNTY HOSPITAL	MICHAEL REESE HOSPITAL	MT. SINAI HOSPITAL
Recovered	182	76	41
Died	14	0	0

compared to the private hospitals. This difference in mortality rates can be explained by the physical state and far-advanced stage of the pathologic condition in the patients who came to the Cook County Hospital. These patients are very often friendless and have no desire or incentive to live on as do the patients in private hospitals. This mental state although an intangible factor is an important one in considering mortality rates. An analysis of the pathology, operative procedure and anesthesia utilized in each patient who died, emphasizes those points to be discussed later as to preoperative preparation, prognosis in certain gynecologic pathology, the character of, and skill employed in the operative procedure as well as anesthesia and postoperative care (Table VIII).

### Discussion

Statistical evidence shows a definite prolongation of the life span. When does old age begin or when is a woman too old to be operated upon are both relative, and answers may be varied and debatable. As Kosmak<sup>4</sup> states, "old age is a relative term and may be designated when decline sets in. Some are more worth while and more competent and better able to take care of themselves at sixty than others at forty. Therefore it would be preferable to measure old age not by years but by competency, both physical and mental."

The question of surgical risk in the old woman has not been properly answered. It was assumed that the elderly individual was unable to tolerate anesthesia or operative procedures. These assumptions have been disproved by the many instances of emergency surgery where the patient was no more disturbed than a younger patient (i.e., torsion of ovarian cyst) and of elective surgery insisted upon by the patient. Since individual experiences were limited, no concerted effort was made to differentiate those women who may be safe operative risks from those who may not be. There are certain general and local conditions which are determinative factors.

TABLE IV. PATHOLOGY IN THE 315 ELDERLY WOMEN

Adenocarcinoma of corpus	24
Squamous cell carcinoma of corpus	2
Fibroids of corpus	43
Fibrosis and adenomyosis	34
Endometrial polyps	9
Squamous cell carcinoma of cervix	1
Leukoplakia of cervix	21
Acanthosis and ulceration of cervix	1
Chronic cervicitis with polyps	33
Tuberculosis of cervix	1
Papillary adenocarcinoma of ovary	16
Multilocular serous cystadenoma of ovary	11
Multilocular pseudomucinous cystadenoma of ovary	5
Multilocular bilateral Brenner tumors of ovaries	1
Fibroma of ovary with cystic degeneration	2
Cystic teratoma of ovary	1
Squamous cell carcinoma of vulva	6
Adenocarcinoma of Bartholin gland	1
Transitional cell carcinoma of urethra	1
Urethral caruncle	1
Pelvic abscess	1
Hematoma of rectus muscle	1
Adenocarcinoma of large bowel (one primary, one secondary)	2

TABLE V. OPERATIONS

Vaginal hysterectomy, anterior and posterior plastic	110
Vaginal hysterectomy, bilateral salpingo-oophorectomy	7
Vaginal hysterectomy and posterior plastic	28
Vaginal hysterectomy and colpoeleisis	3
Watkins' interposition and posterior plastic	7
Vaginal defundation	1
LeFort and posterior plastic	24
Manchester plastic and posterior plastic	4
Cervicectomy, anterior and posterior plastic	10
Cervicectomy and colpectomy	1
Total colpoeleisis and posterior plastic	2
Anterior and posterior plastic	38
Partial resection of urethra	1
Abdominal hysterectomy	1
Subtotal hysterectomy	3
Subtotal hysterectomy and bilateral salpingo-oophorectomy (Two with appendix)	18
Abdominal total hysterectomy, bilateral salpingo-oophorectomy	21
Abdominal fixation of corpus uteri	1
Abdominal fixation of vaginal vault	1
Exploratory laparotomy	8
Dilatation and curettage, bilateral salpingo-oophorectomy	1
Unilateral oophorectomy	17
Bilateral oophorectomy	2
Vulvectomy (3 with Bassett operation) (Stoeckel)	8
Ventral herniorrhaphy	1
Closure of colostomy and left oophorectomy	1
Incision and drainage of rectus hematoma	1
Resection of colon and first stage Mikulicz	1

in this age group. vaginal hysterectomy further seems the most desirable operative procedure for the prolapsing uterus. The variety of gynecologic operations indicates the feasibility of performing any type of gynecologic surgery in this age group.

The choice of anesthetic is indicated by the high incidence of local anesthesia (1 per cent procaine) in Table VI.

The immediate postoperative results indicated in Table VII reveal the unusual high incidence (7 per cent) of deaths in the Cook County Hospital as

Kidney function should be tested in every case. A simple measure is the concentration test. If the specific gravity of the urine rises above 1.020, the kidney function is fairly adequate; if it remains between 1.015 and 1.020, there is impairment of renal function. Specific gravity that remains below 1.015 indicates serious renal damage. Determination of the urea nitrogen of the blood gives further information.

A complete blood count should be carried out preoperatively, since secondary anemia is common in old women. These hypochromic secondary anemias can be readily remedied. The general nourishment may be augmented by iron and the vitamins, especially the B complex. Transfusions may be employed to overcome anemias in urgent cases, as well as to increase the proteins of the blood.

Preoperative sedation must not be too great, since older individuals are readily depressed, and respirations become very slow, therefore barbiturates are preferable to morphine. Also, liver function being decreased, there is a decreased excretion of drugs, and therefore they are retained longer and have an accumulative effect. Intravenous pentothal is not considered safe.

Local (procaine) anesthesia is the most desirable anesthetic because it is the safest and is well tolerated by old people. Combination of pudendal block and local infiltration will allow the performance of any vaginal operation. Of the inhalation anesthetics, cyclopropane or ethylene with oxygen come next, then nitrous oxide and ether. Ether is well tolerated by cardiopaths.

The operative procedures must be rapid, precise, with little trauma or shock-producing manipulations. If proper hemostasis is accomplished with accurate approximation of tissue without strangulation, healing occurs readily. Vitamin C is believed to be of aid in the healing of the wounds.

Postoperative complications that occur with particular frequency among old patients are local wound infections, bronchopneumonia, urinary tract infections, thrombosis of the peripheral veins, and pulmonary embolism, cardiac infarction, and psychoses. Early mobilization of the patient is one of the best means of preventing most of these untoward events. The position of the patient in bed should be frequently changed, and she should be compelled to flex and extend her legs at frequent intervals. She should be allowed out of bed at the earliest possible moment. It is of interest to call attention to the fact that early ambulation postoperatively was first started among old patients, and now is becoming more generally used in all postoperative patients. Early postoperative ambulation has definite advantages, as determined by personal observations and by observations of others.<sup>16</sup> Steinhart<sup>16</sup> reviewed the literature and studied a small controlled postoperative series.

The mortality rate in old people treated surgically is higher than in young people; in view of the pathology and the senile changes present. Since the risk is greater, the individual patient must be thoroughly studied, as discussed above. If conditions allow, proper preparation may decrease the risk of surgery. Sanders and Sellers<sup>17</sup> report a gross fatality rate of 1.8 per cent in 1,000 gynecologic operations in women of all ages. Sanders,<sup>18</sup> in a later series of 500 patients, had a 0.2 per cent rate. In 6,022 operations performed on the gynec-



At the initial consideration of surgery in the aged, the life expectancy must be weighed against the mortality rate of the operation. The mental state of the patient and outlook in life are important, and here the psychologic effect of the surgeon's approach may determine whether the patient will be optimistic and courageous or feel the approach of her doom. This state of mind, although intangible, can be evaluated with a little time spent conversing with the patient. She objects to any great changes in her daily routine, and therefore all effort should be made, if possible, to adhere to her daily routine.

According to Thewlis,<sup>3</sup> surgical procedures in aged patients present many peculiarities. These include constitutional changes, greater resistance to infection when the individual is in fairly good condition, and considerably lowered resistance to infection when the body is debilitated; with more severe surgical shock, slower reaction from the shock; there may be lessened power of repair, cardiac and respiratory degeneration, and increased danger from anesthesia.

Taking full cognizance of the above constitutional peculiarities of the aged, when surgery offers the best result in a certain gynecologic condition, it is evident that the following steps must be taken to make the patient prepared for the operative procedure. A painstaking physical examination is essential to establish proper oral hygiene and eliminate infected teeth; to determine the adequacy of the cardiac reserve and coronary artery sclerosis by roentgen and electrocardiographic studies. Brumm and Willius<sup>15</sup> reported on 257 patients with severe coronary artery disease who underwent necessary surgical operations. The average age was 60.3 years, 32 patients had healed infarcts at the time; in 100 cases there was well-marked arterial hypertension; eleven patients (4.3 per cent) died of cardiac causes. Some observers wait for two or three months after an attack before operating on a patient.

In addition to the cardiovascular status study, respiratory tract examination, renal function evaluation by urinary secretions, and blood chemistry determinations and blood picture scrutiny are all important steps toward making the decision, whether surgery may be considered reasonably safe. When a pathologic condition is found, an opinion as to the seriousness of the medical condition may be sought from a competent internist. We have already learned that hypertension without serious cardiac complication does not add much to the hazards of operation. Eighty per cent of the series studied had hypertension and probably a certain number would be benefited, since 73 per cent had some form of pelvic herniosus. The question of anesthesia in hypertensive patients comes up for consideration. Local, regional or low spinal anesthesia is well tolerated. In cardiopaths, ether anesthesia can be used, while spinal is best avoided, although local may be employed.

Pulmonary emphysema and fibrosis and chronic bronchitis may favor the development of postoperative pneumonia; however, with serious pulmonary impairment, local or regional anesthesia may be best. In some cases cyclopropane or ethylene with oxygen may be used. Postoperative oxygen inhalation and frequent changing in position as well as early rising from bed are desirable procedures.

all deaths occurring in the Cook County Hospital patients. The difference in mortality rates is very striking, and definite reasons can explain it. The seriously ill and poorly nourished women with relative avitaminosis are more common in a public hospital like Cook County than in any private hospital. Thus, again the significance of the proper preoperative preparation of the patient is emphasized. The operative mortality rate in the old gynecologic patients is double (7.6 per cent) that of the series of all ages (3.5 per cent) at Cook County Hospital (Greenhill<sup>10</sup>). In analyzing the 14 deaths, the causes of death indicate that with our present chemotherapy and more available blood for transfusions, the mortality rate would have been decreased today. Fifty per cent of the deaths were due to sepsis. Only one death was due to post-operative shock and, in this instance, a 74-year-old woman was subjected to ether anesthesia. Embolism produced death only once. Cardiac failure accounted for two deaths, uremia for one, pneumonia for one. The far advanced anaplastic carcinoma of the ovaries with peritoneal carcinomatosis was the cause of one of the deaths rather than the surgical procedures (Table VIII).

### Conclusions

1. Gynecologic surgery may be performed in old women (past 60 years) under urgent, imperative, or elective conditions with proper preoperative precautions, selection of anesthesia (especially local), careful, meticulous operative procedures, and proper postoperative care.

2. The higher mortality rate in older people was due to sepsis, shock, embolism, pneumonic infections, uremia, cardiac failure, but also due to the higher incidence of malignancies. With chemotherapy and blood transfusions, the most common operative complication may be combated.

3. Hypertension without marked cardiac damage is no great hazard. It may be improved by overcoming the partial ureteral obstruction and its resultant effect on the kidneys, in the correction of pelvic herniosus with the prolapsing uterus.

4. The relief experienced by an old woman with procidentia with good life expectancy more than balances the risk involved in the surgical care, thus adding a happy comfortable life to her years.

I am indebted to Doctor S. R. Lash and Dr. P. Grossbard for their aid in reviewing some of the patients' records.

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TABLE VIII. BRIEF RÉSUMÉ OF DEATHS

NAME	AGE (YEARS)	CLINICAL OR PATHO- LOGIC DIAGNOSIS	OPERATION ANESTHESIA	DAY AND CAUSE OF DEATH
M. K.	74	Procidentia uteri	Vaginal hysterectomy. Anterior and posterior plastic. Ether and nitrous oxide	Nine hours postopera- tive—shock
B. C.	65	Procidentia uteri; leu- coplakia of cervix	Vaginal hysterectomy. Local	3rd day postoperative; pulmonary embolus, bronchopneumonia
K. M.	70	Adenocarcinoma of left ovary	Left salpingo-oophorec- tomy. Ether-nitrous oxide.	22nd day postoperative. Sepsis
S. W.	60	Inoperable adenocarci- noma of ovaries	Exploratory, biopsy of mass; ether-nitrous oxide	28th day postoperative. Sepsis; pyelitis
C. D.	67	Procidentia uteri; hemi- plegia 216/110	LeFort perineorrhaphy. Local	3rd day postoperative. Hypostatic pneumonia
N. C.	68	Large papillary cystade- noma of ovaries, ar- teriosclerosis, myo- carditis	Subtotal hysterectomy; bilateral salpingo- oophorectomy. Spinal	65th day postoperative. Decompensation of heart; terminal hypo- static pneumonia
J. S.	73	Large ovarian cyst with abscess	Laparotomy; incision and drainage. Nitrous oxido	38th day postoperative. Phlebitis of left leg; sepsis
E. N.	78	Diabetes; procidentia uteri	LeFort. Local	13th day postoperative. Pneumonia
A. B.	73	Procidentia uteri; hyper- tension 208/120	Vaginal hysterectomy; perineorrhaphy. Ni- trous oxide.	7th day postoperative. Uremia
B. S.	76	Procidentia uteri; ulcer of cervix; leukoplakia; chronic myocarditis	Vaginal hysterectomy; anterior and posterior plastic. Local	7th day postoperative. Sepsis
G. W.	70	Infiltrating squamous cell carcinoma of ure- thra; inguinal gland metastasis	Radical vulvectomy. Local	18th day postoperative. Sepsis
C. B.	79	Procidentia uteri; hemi- plegia	LeFort. Local	Discharged on 12th postoperative day; no home; remained in hospital and died on 40th postoperative day of hypostatic pneumonia
A. B.	68	Anaplastic carcinoma of ovaries	Exploratory; biopsy of omentum. Metastases to liver and peri- toneum. Spinal	39th postoperative day. Progressive downhill course
M. C.	70	Torsion of right ovarian cyst; carcinoma of rec- tum; fibroids of uterus; arteriosclerotic myo- carditis	Subtotal hysterectomy; bilateral salpingo- oophorectomy. Spinal	1st postoperative day. Cardiac failure

cologic service of the Cook County Hospital, Greenhill<sup>19</sup> found a mortality rate of 3.5 per cent. At the Mayo Clinic,<sup>20</sup> in the years 1939 and 1940, 1,364 operations were done on 1,204 patients aged 65 years or over, with an operative mortality of 9 per cent. In those aged 65 to 74, the mortality was 8 per cent. in those 75 to 79, it was 13 per cent, and in those over 80, it was 35 per cent. In operations for prolapse of the uterus in 441 patients of all ages, the Michael Reese Hospital<sup>21</sup> mortality rate was 1.6 per cent. The mortality rate in the 313 patients (Table VIII) reported was 4.5 per cent:

## STRESS INCONTINENCE IN THE FEMALE\*

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URINARY incontinence in the female may arise from a variety of causes. It may be associated with congenital defects, with neurogenic abnormalities, or with trauma, usually incident to parturition. Such trauma may result in fistulas, in destruction of the urethra, or in herniation, i.e., urethrocele and/or cystocele. However, examination of the incontinent patient may reveal little or no external evidence of perineopelvic damage. And conversely, a large cystocele, a protruding urethrocele, even complete prolapse, may exist and the patient remain continent—sometimes to become incontinent after the pelvic floor is repaired.

This study is a consideration of the various factors concerned with the involuntary escape of urine through the intact urethra, and their treatment. Incontinence associated with obvious etiologic factors such as fistulas, nerve lesions, and congenital anomalies will not be considered. The actual urine loss may vary from only a few drops at the time of sudden increase in intravesical or intra-abdominal pressure to complete incontinence, even when recumbent. Complete incontinence is rarely encountered, but partial incontinence brought on by sneezing, coughing, or straining is all too common. It is to this type of incontinence that the word "stress" is applied.

A lack of uniform interpretation of perineopelvic anatomy still exists. Even the physiologic process of micturition and the pathologic physiology involved in incontinence are imperfectly understood. Unanimity exists only in the observations that this type of incontinence is frequently encountered in middle-aged multiparas, that it is an embarrassing, unpleasant incapacity, and that, although many operations have been devised, the treatment is often unsatisfactory. It is remarkable that, although the methods of treatment vary widely in both anatomic and physiologic approach, the end results have all been similar. Approximately 80 per cent of the patients are cured by any one of the many procedures advocated. Our study will attempt to explain why various types of repair meet with similar success.

Confusion and misunderstanding arise from the multiple terminology of a given anatomic structure; thus, the external voluntary urethral sphincter is variously known as the sphincter urethrae membranaceae, the sphincter urogenitalis, the compressor urethrae, the constrictor urethrae, the deep transverse perineal muscle, and the muscle of micturition. Some authors consider the sphincter urethrae membranaceae and deep transverse perineal muscle as separate entities, while others consider them as one and the same. We shall refer to this structure as the external urethral sphincter. These muscle fibers lie between two connective tissue sheets, and the entire formation which we will

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urethra. These layers consist of voluntary striated muscle, with their fascial coverings. From within outward they are known to us as the pelvic diaphragm, the urogenital diaphragm, and the superficial diaphragm. The superficial diaphragm is divided into three distinct bundles, the bulbocavernosus, the ischio-cavernosus, and the superficial transverse perineal muscle.

The bulbocavernosus is a museulofibrous sheath investing the vestibular mass of erectile tissue that lies in each labium majus. It arises from the posterior perineal body and divides into two superficial portions, one inserting in the corpus cavernosus of the clitoris with a fascicular band crossing the body of the clitoris, and a deeper portion that inserts into the urethra (Davies<sup>4</sup>).

The urogenital diaphragm consists of the external urethral sphincter and its two layers of fascia. These fibers arise from each side of the inner surface of the ischiopubic ramus, and pass medialward to insert in a median raphe, passing above and below the urethra, as well as supplying fibers to the urethra, vagina, and rectum (Fig. 1).

In the region subjected to perineal surgery, the urogenital diaphragm and the inner margin of the pelvic diaphragm (pubococcygeus) are in apposition, giving rise to the familiar muscular band so readily felt on vaginal examination, and usually referred to as the levator pillar or pubococcygeus. According to Curtis, the major part of this band is actually derived from the urogenital diaphragm, but through common usage this surgical entity is so often called the levator. We will refer to it as the pubococcygeus. It will thus be seen that median fibers from the pubococcygeus also reach the urethra, the vagina, and the rectum, and descend upon each of these structures, blending with the intrinsic muscular coat. Thus, the urethra is separated from the vagina by a museulofibrous sheath which contains fibers from the pelvic, urogenital, and superficial diaphragms, as well as smooth muscle fibers from the internal sphincter. From a practical viewpoint, the levator ani and its fascia are closely inter-related with the perineal sphincters and, by fixating the pelvic diaphragm, the levators synergize and coordinate the activity of the sphincters.

The structures which support the uterus at a higher level are also important. These thickenings of the endopelvic fascia, the cardinal ligaments, are blended with the adjacent structures. The innermost fibers of the cardinal ligaments pass to and around the cervix into the pubovesicocervical fascia.

The nerve supply of the bladder and internal sphincter consists of an intrinsic nerve plexus with outlying ganglion cells and fibers that have been shown to be capable of functioning after all other nerve fibers are destroyed. In addition, they receive sympathetic fibers from the hypogastric nerve (presacral nerve) and inferior mesenteric ganglion, and parasympathetic fibers from the second, third, and fourth sacral nerves by way of the pelvic nerves (nervi erigentes). The voluntary urethral sphincter and the associated voluntary pelvic and perineal muscles are innervated by the pudendal nerves (somatic) derived from the sacral (3 and 4) portion of the cord.

The physiologic mechanism of micturition involves the concept of the opening of both the involuntary and voluntary sphincters at an appropriate time. According to Denny-Brown,<sup>8</sup> the lumbosacral segment contains all of the nervous mechanism necessary for micturition except that which decides whether its occurrence would be appropriate to the environment. The latter is provided by the higher centers. In the normal female the internal sphincter alone can retain urine within the bladder. The sphincter is closed, but not in a state of con-

refer to as the urogenital diaphragm is also termed the urogenital trigone, or the triangular ligament.

Then there is the musculo-fibrous tissue extending from the pubis to the cervix. It is referred to as the median fibers of the pubococcygeal portion of the levator ani, as the pubocervical fascia, as the pubocervical muscle sheet, vesicovaginal fascia, and as the pubovesicocervical sheath or fascia. We shall refer to this tissue as the pubovesicocervical fascia.

One author uses one appellation, another an entirely different one, and the reader becomes more and more lost. This confusion in terminology is a reflection of lack of uniform anatomic understanding. The structures that one investigator describes may not be apparent to another, or may be interpreted differently and called by another name. Further difficulty arises from the fact that fibers from several different structures are fused in the region of the urethra. We shall see that fibers from the pubovesicocervical fascia, the urogenital diaphragm, and the pubococcygeus form a single layer around the urethra.

The anatomic findings of cadaver dissection differ greatly from those demonstrable at the operating table. Likewise, the structures revealed by dissection of the perineum of the nulligravida differ from those of the multigravida. Curtis, Anson, and Ashley<sup>1</sup> have contributed a great deal to a rational understanding of pelvic structures. In addition should be mentioned the magnificent illustrations of Max Brödel<sup>2</sup> and the anatomic contributions of Johnston,<sup>3</sup> Davies,<sup>4</sup> Kennedy,<sup>5</sup> and others.

The bladder and urethra are surrounded by a loose areolar tissue which is an extension of the endopelvic fascia. This periurethral tissue is condensed on the ventral surface to fix the urethra and vesical neck to the undersurface of the symphysis pubis, while on the dorsal surface it becomes continuous with the pubovesicocervical fascia. Three smooth muscle layers are described in the urethra, an inner and outer longitudinal, and a middle circular. These layers are continuous with the bladder musculature. At the vesical neck the muscle is thickened and somewhat differentiated into a set of interlocking loops and circular fibers (Van Duzen and Looney<sup>6</sup>), referred to as the internal urethral sphincter, but also called the sphincter vesicae or the lissosphincter (Martius<sup>6</sup>). The fibers of this involuntary sphincter muscle pass in an oblique direction and extend into the fibrous sheath between bladder and vagina, as well as into the vagina. A strong group of longitudinal muscle fibers arise on the posterior bladder wall in the area between the ureteral orifices and pass downward, through the internal sphincter, to intermingle with the longitudinal fibers of the urethra. This muscle, the trigonalis, was well described in the male by Young and Wesson<sup>7</sup> and plays a most important role in the physiology of micturition. The mucosa of the urethra is thrown into longitudinal ridges which make marked dilatation possible without injury. Between mucosa and muscularis is a cavernous vascular submucosa, the erectile tissue, or corpus spongiosum of the urethra.

As the urethra penetrates the three muscle layers of the pelvic outlet, fibers from each of these muscular layers become intimately associated with the

so that there is no further leakage. This type of ineontinence is evident, particularly when the bladder is partially distended. Coughing, sneezing, or moving suddenly causes ineontinence, but continuation of the same process does not cause repeated urine loss.

The third barrier, the superficial pelvic diaphragm, is also brought into play reflexly at the same time as the external sphincter.

Continence is further maintained by the slight mechanical barriers imposed, consisting of the abundant mucosa in folds and the erectile tissue of the submucosa, both structures narrowing the lumen. Angulation of the urethra at the vesical neck is believed by Taylor and Watt<sup>10</sup> and others to provide additional resistance. The excellent studies of Barnes,<sup>11</sup> however, do not confirm a constant relationship between angulation and ineontinence, but demonstrate that a wide variation in urethral angulation occurs in continent patients.

The causes of ineontinence are many. Any factor that either increases the urinary expulsive force or the intravesical pressure or lowers the powers of resistance can cause ineontinence. Until recently, most emphasis has been placed on damage to the internal sphincter. That trauma during childbirth is an important factor is logical from the observations (Taylor and Watt<sup>10</sup>) that the great majority of women with stress ineontinence have had children, and that the incidence of ineontinence rose with the number of children delivered. That damage to the internal sphincter is not the sole cause, if cause it be, is indicated by the fact that resection of the bladder neck is not necessarily followed by ineontinence. Watson<sup>12</sup> believed the lack of control was due to relaxation of the fascia supporting the neck of the bladder, but not damaging the sphincter itself. By replacing the bladder neck to its normal position behind the pubis, he was able to cure many patients. Johnston<sup>3</sup> and others believe that damage, either through stretching, tearing, or necrosis, of the urogenital diaphragm is responsible for ineontinence, the internal sphincter usually being uninjured during childbirth and, at best, being a small, weak muscle. Kennedy<sup>13</sup> believes that the ineontinence is associated with damage to the supporting structures plus adhesions distorting the urethra and fixing it to the margin of the pubic rami. In a later publication (1941), Kennedy<sup>14</sup> adds that the sphincter mechanism can be satisfactorily restored by plicating and replicating the undersurface of the urethra, and that the sphincter mechanism requires no assistance of the levators and the vaginal wall.

It is apparent that there are different concepts as to the mechanism of stress ineontinence. They vary from damage to the internal sphincter to damage of the external sphincter and the supporting structures of urethra and bladder. It seems probable that ineontinence is not the result of any one cause, but may result from one or another cause, or from several. It is further probable that the damage incident to parturition involves in varying degree, by stretching and tearing, all the structures associated with the bladder and urethra. The shutoff mechanism can apparently withstand many insults without breakdown, and the final outcome depends not only on the damage inflicted, but also on the constitution of the tissues subjected to the trauma.

There are many generic types of operations which have been advocated and used in the treatment of stress ineontinence. One of the earliest to meet with success was advancement of the urethra as devised by Pawlik, and later modified by Dudley.<sup>15</sup> Torsion of the urethra was advocated and practiced by Gersuny, and later modified and combined with advancement by Ries. Both the Dudley and Ries operations are still described in detail in modern operative gynecologic textbooks (Crossen and Crossen<sup>16</sup>). In 1913, Kelly<sup>17</sup> advocated shortening the internal sphincter with a mattress suture, and to this day this operation is probably the best known and most frequently used. Watson<sup>12</sup> advocated care-



tinuous contraction. If, however, it is gradually distended, it will contract—the force exerted being proportional to the degree of distention. Relaxation of the internal sphincter and urethra is brought about by contraction of the bladder, the arching trigone bundle opening the passage by its down pull (Van Duzen and Looney<sup>5</sup>). As the bladder is emptied, the sphincter again gradually returns to its closed state. This reciprocal bladder-sphincter mechanism is apparently dependent on the intrinsic nervous plexus. Division of the presacral nerve (sympathetic) will cause paralysis of the trigone muscle and delay in starting the stream, because now increased intravesical pressure alone must open the sphincter. Royston and Rose<sup>9</sup> have stressed the importance of repair of the trigone muscle in those patients who have suffered injury to that structure. Van Duzen<sup>31</sup> advocates presacral neurectomy in obstinate cases of stress incontinence in which other measures have failed.

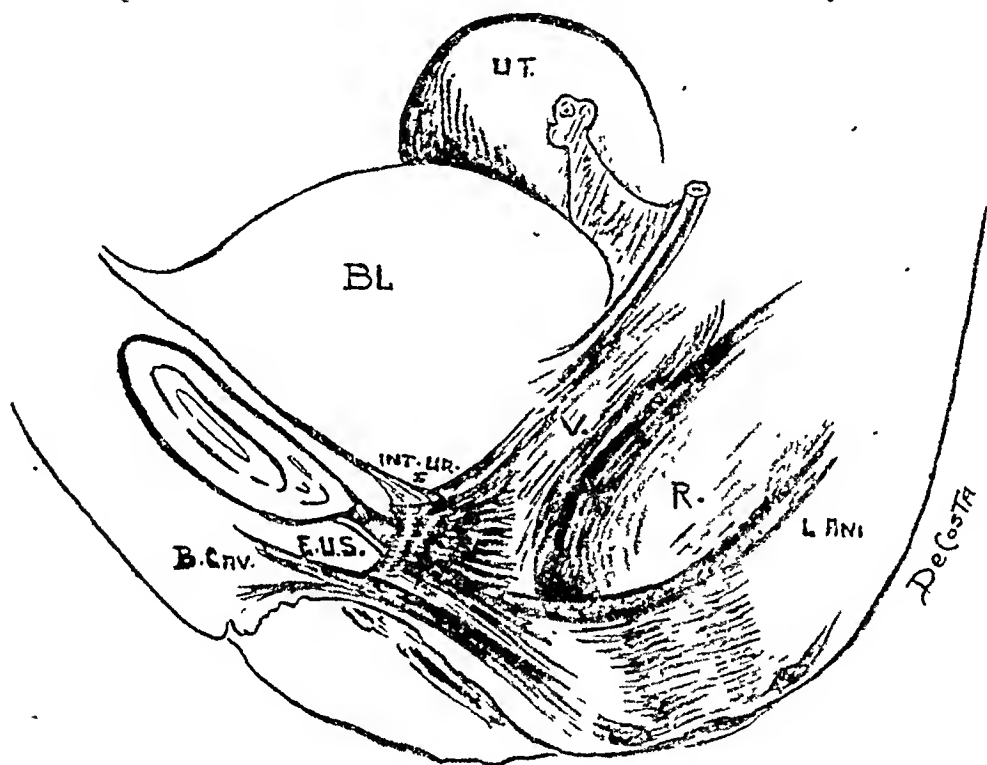


Fig. 1.—The external urethral sphincter (E.U.S.) and its relationship to adjacent structures: *B.Cav.*, bulbocavernosus; *BL.*, bladder; *INT.UR.S.*, internal urethral sphincter; *L.ANI*, levator ani muscle; *R.*, rectum; *UT.*, uterus; and *V.*, vagina.

The external sphincter is a compact, quick-acting muscle that is capable of rapid reflex action. Ordinarily it is relaxed, but is brought into play when there is a sudden rise in intra-abdominal and, hence, intra-cystic pressure. It has been shown that a sudden, moderate rise in intravesical pressure will not force open the normal internal sphincter, hence the external sphincter may not be necessary unless the internal mechanism is weakened or the rise in pressure is marked. With internal sphincter damage, the external sphincter is usually sufficient to preserve continence. However, damage to the latter removes the second barrier and a rise in vesical pressure associated with effort, coughing, sneezing, laughing, even quick motions, may be followed by urinary loss.

At times the damage to the sphincter mechanism may be manifested as a delay in the reflex reaction of the voluntary muscle, the incontinence occurring only at the very onset of increased pressure. Later control causes adjustment,

the mucosa is made encircling the external urinary meatus. This is kept 0.5 cm. from the orifice to leave an ample cuff for subsequent suturing. That portion of the mucosa contained between the two incisions is removed by sharp dissection, thus denuding the entire area (Fig. 3).

The urethra is picked up by toothless forceps and pulled upward toward the clitoris. This puts the urethral wall under tension, and makes the urethral dissection easier. The urethral wall is dissected free from the underlying structures (Fig. 4). This is accomplished by "scraping" the tissues away from the urethral wall by means of a sharp scalpel. This procedure is carried back along the urethra toward the bladder until the urethra has been freed sufficiently to allow the dissected external meatus to lie just under the clitoris without traction. Such a dissection by "scraping" seems hazardous, but there has been no urethral injury in any of our patients. We believe that urethral injury is more likely to result when a catheter is used. The "scraping" dissection results in moderate and continuous venous oozing, but experience has shown that hemostasis is unnecessary and time-consuming at this point. Satisfactory hemostasis is always obtained subsequently by the sutures which are used to unite the pubococcygeus and bulbocavernosus muscles.

The urethra is now anchored just below the clitoris by three interrupted mattress sutures. Chromic catgut No. 00 is used throughout the operation. This upward placement and suturing of the urethra brings into view the pubococcygeus muscles which are now united in the midline beneath the urethra by two to four interrupted sutures (Fig. 5). The bulbocavernosus muscles are then united in the midline, thus completing the second layer of sutured muscles which hold the urethra upward (Fig. 6). The cut edges of the mucosa are united to the cuff about the urethral orifice by mattress sutures. Several sutures are also used to unite the mucosa in the midline (Fig. 7).

An indwelling catheter is inserted and remains in place for five to seven days. It is used because the postoperative edema about the external urinary meatus makes catheterization difficult, even when attempted by someone experienced with this type of operation. Resultant trauma might tear out the delicate superficial sutures and thus undo the entire operation.

The operation here described and as originally described by Berkow is not difficult and can be quickly performed. It may be carried out as a single procedure, or may be combined with a cystocele repair, vaginal hysterectomy, or both. The vaginal hysterectomy and/or cystocele repair should be performed first and followed by the paraurethral fixation. Colpo-perineorrhaphy, when indicated, should be performed last.

Convalescence is short and usually uneventful. The patients are permitted out of bed after the first forty-eight hours. They may be ambulatory, even though the indwelling catheter is in place. This can be accomplished by disconnecting the catheter from the suction apparatus to which it is usually attached and corking the free end of the catheter.

Para-urethral fixation has been performed 33 times by us during the past five years. The 33 patients ranged in age from 23 to 82 years. Twenty-nine were parous women, and the stress incontinence was obstetric in origin. Four were nulliparous, and the two failures in our series both occurred in this group. Patients were followed for periods ranging from five to fifty-four months postoperatively.

Preoperative examination showed that 17 patients had a urethrocele. In the remaining 16 patients, stress incontinence was present, but no definite urethrocele was demonstrable. Of the entire group, 13 had a cystocele, five had second or third degree uterine prolapse, four had complicating fibroids of the uterus, and two had cervical and uterine polyps.

ful imbrication of the fascial supports of the bladder, restoring the bladder to its normal position behind the pubis and correcting the cystocele. Bissell<sup>18</sup> utilized the muscular layers of the vagina to support urethra and bladder neck. Frost<sup>19</sup> mobilized the urethra and bladder, pliated these structures without tension, and re-enforced this repair by strips excised from the anterior vaginal wall sutured under the vesical neck to the undersurface of the symphysis. The use of fascial strips or fascia and muscle strips derived from anterior abdominal wall muscles to produce a sling under the urethra has been advocated by Goebell,<sup>20</sup> Stoeckel,<sup>21</sup> Miller,<sup>22</sup> Aldridge,<sup>23</sup> and others. Deming<sup>24</sup> transplanted the gracilis muscle. Lowsley<sup>25</sup> imbricated the bulbocavernosus above the urethra. Martius<sup>26</sup> transplanted the bulbocavernosus beneath the urethra. Taussig<sup>27</sup> transplanted strips of the levators beneath the urethra. Berkow<sup>28</sup> advocated urethral advancement and approximation of the bulbocavernosus and pubococcygeus beneath the urethra. Kennedy<sup>29</sup> stressed the importance of subpubic adhesions and distortions of the urethra. In his operation, these adhesions are freed, the urethra pliated in the midline to prevent further adhesions forming, and the "sling fibers" joined below the urethra.

In analyzing the various procedures employed, we note that one of several mechanical changes is made: (1) the urethra is lengthened or twisted, thereby decreasing its lumen and, by stretching, increasing its tone; (2) the urethra and/or bladder are returned to their normal position behind the pubis, re-establishing the urethrovesical angle and tightening the fascial support; (3) the musculature of the bladder neck and/or urethra is pliated, decreasing the lumen and strengthening the fascial support; or (4) a musculofascial sling is placed below the urethra, which (a) by mere pressure narrows the canal, (b) provides additional support for the urethra, and (c) may function by voluntarily contracting the urethra when stimulated, and (d) tightens the fascial supports. No matter what the explanation for success given by the author, *all procedures have in common the tightening of the fascial planes through which the urethra and vagina pass*. This even applies to advancement or torsion of the urethra, because the fibers from the levators, urogenital diaphragm, and superficial diaphragm, even the internal sphincter, are stretched by these procedures. The fascial supports of the pelvic floor are further tightened by the customary procedure of repairing cystocele or rectocele, if present.

In the paraurethral fixation operation described by Berkow, the urethra is advanced and slightly angulated, thereby narrowing the lumen, increasing the length of the urethra, and increasing the tension of all the fibers it receives from adjacent structures. The pubococcygeus muscles are approximated below the urethra. Further support is given by uniting the two bulbocavernosus muscles as a second layer, thus creating a strong anterior muscular support. With the colpoperineorrhaphy the fascial layers are further tightened. Imbrication of urethra and/or bladder neck is not employed. Actually, imbrication, including Kelly's internal sphincter plastic, can be considered as merely another method of tightening the supporting fascia.

### Technique

The patient is placed in lithotomy position and the labia minora are sutured laterally for exposure. A traction suture is placed just below the clitoris. A second traction suture is placed four to five centimeters below the external urinary meatus. The mucosa of the vestibule is then picked up by two Allis forceps on either side of, and one to two centimeters below, the urinary meatus.

Sustained traction on the two Allis forceps and on the two traction sutures outlines a quadrilateral area which includes the vestibule and anterior vagina, and brings these structures into a single plane. A diamond-shaped incision is made outlining this quadrilateral area (Fig. 2). A second incision through

Paraurethral fixation was performed in all 33 patients. This was the only operative procedure in 13 women who had no complaints other than stress incontinence and no complicating pelvic pathology. Multiple operative procedures were performed in the remaining 20 women. These included 14 anterior colporrhaphies and 11 colpoperineorrhaphies, seven vaginal hysterectomies, two abdominal hysterectomies with bilateral salpingo-oophorectomy in each, and two polypectomies.

An indwelling catheter was used postoperatively in each instance, for an average length of time of six days. There was no morbidity referable to this procedure, and bladder function following removal of the indwelling catheter was normal in seventeen. Catheterization was necessary once in 13 patients, twice in two, and six times in one patient.

The average hospital stay for the 13 patients who had paraurethral fixation only was ten days, while the average hospital stay for the entire group was twelve days.

There was no postoperative morbidity in 26 patients, while seven ran a febrile course. One patient, a 50-year-old para ii, developed fever and cough on the third day following abdominal hysterectomy, bilateral salpingo-oophorectomy, and paraurethral fixation. These complaints persisted for one week, and were probably due to a pulmonary infarct, although neither the physical findings nor roentgenography were conclusive. This patient was discharged on the thirteenth postoperative day. Her cough persisted for two months, during which time there was a continuation of the stress incontinence. As the continuous hacking cough disappeared, her bladder symptoms disappeared, and, at follow-up examination three months later, she was completely continent.

Postoperative thrombophlebitis occurred once. The patient was a 39-year-old para v who had urethrocele, cystocele, rectocele, and multiple uterine fibroids. A vaginal hysterectomy, anterior colporrhaphy, and posterior colpoperineorrhaphy followed by paraurethral fixation resulted in a febrile convalescence lasting twenty-three days because of thrombophlebitis of the left leg.

A final operative complication is of interest because it emphasizes the importance of careful preoperative diagnosis. The patient, a 52-year-old para iii, complained of marked incontinence for the past two years. It began immediately following a total abdominal hysterectomy to remove uterine fibroids. Loss of urine followed almost any type of activity, but never occurred when lying down. There was definite loss of urine from the urethra on straining or coughing. Careful urologic examination, including cystoscopic examination of the bladder, revealed no abnormality. Postoperatively, incontinence persisted after removal of the indwelling catheter. Cystoscopic examination four weeks following the paraurethral fixation disclosed a small vesicovaginal fistula. This was repaired five weeks after the first operation with good results. It seems improbable that the vesicovaginal fistula resulted from the paraurethral fixation, for the area of the bladder involved in the fistulous tract was at a considerable distance from the urethra. It is much more likely that the vesicovaginal fistula followed the abdominal hysterectomy, and that our preoperative diagnostic methods failed to reveal its presence. If the fistula had been detected, as it should have been, it would have been corrected and the paraurethral fixation then performed.

All patients were examined four to six weeks postoperatively. At this early date, about one-half still have some degree of impairment. This decreases gradually during the next three to four months. Examination of the 33 patients in this series at the end of four months showed complete continence and urinary control in thirty-one. Apparently considerable time must elapse to achieve complete success with this operation. The resultant scar formation and tissue

Fig. 2.



Fig. 3.



Fig. 4.



Fig. 5.



Fig. 6.



Fig. 7.



Fig. 2.—The labia minora have been sutured laterally, and traction sutures have been placed below the clitoris and in the anterior vaginal wall. The quadrilateral area of the vestibule and anterior vaginal wall is thereby outlined. The diamond-shaped incision and encircling urethral incision have been made.

Fig. 3.—The vestibular mucosa has been excised.

Fig. 4.—The urethra has been carried anteriorly and freed from the underlying tissue.

Fig. 5.—The pubococcygeus muscles have now been approximated. The needle has been inserted through the bulbocavernosus for the placement of the first suture in the second layer.

Fig. 6.—The bulbocavernosus muscles have been united beneath the urethra.

Fig. 7.—The mucosa has been united by the addition of several mattress sutures, thereby completing the operation.

5. Paraurethral fixation was carried out in a series of 33 patients suffering from stress incontinence.

6. It was completely successful in 31 patients, the only two failures occurring in women in whom the etiology of the stress incontinence was not obstetric.

7. Paraurethral fixation is a most satisfactory operation for the relief of stress incontinence following obstetric injury.

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retraction take twelve to sixteen weeks. Likewise, time is a factor in the development of urinary control. It is essential to advise such patients that complete continence may not be obtained for several weeks. Failure to inform them will lead to some unhappiness for the first few postoperative weeks.

The patients must also be informed of the resulting change in the direction of the urinary stream. Following paraurethral fixation, the dislocated external urinary meatus causes the stream to be more horizontal than normal. This may result in wetting and annoyance. It can be completely overcome by tilting the body forward during micturition. The patient must be forewarned and taught to lean forward while voiding.

Two patients developed cystitis and recurring stress incontinence twelve and twenty-four months following paraurethral fixation. Both responded to chemotherapy plus urethral dilatation and urethral massage. A Walther urethral dilator is inserted into the urethra, and the dilated urethra is massaged rather vigorously through the anterior vaginal wall. Dilatation with massage is done twice weekly for two to four weeks, and apparently helps to restore normal tissue tone. This procedure also seems to be of value during the period of late convalescence, i.e., six to twelve weeks postoperatively. Dilatation with massage apparently speeds up the return to complete urinary control. It was carried out in six patients with beneficial results.

One patient became pregnant and has delivered two full-term babies without the recurrence of stress incontinence. When last seen on June 21, 1946, she was again pregnant, but completely continent.

There were two complete failures in this series of 33 patients. One was an 82-year-old nullipara who had anteroposterior suturing following total colpocleisis rather than side to side closure. The resultant pull on the urethra produced stress incontinence. Paraurethral fixation was performed, but gave absolutely no relief of the distressing symptoms.

The second failure occurred in a 48-year-old nullipara. This patient had been treated for incontinence over a period of twelve years with varying degrees of success. Some four years ago the Kelly operation was performed which relieved her symptoms for a few months. Estrogenic substance in varying dosage also afforded temporary relief. Urologic examination failed to disclose any abnormality, and gynecologic examination was not significant. The patient was depressed, frustrated, and unhappy. She was not willing to consult a psychiatrist, but it was hoped that paraurethral fixation would solve her difficulties. As with the Kelly operation, she received relief for a period of about three months. It is believed that her incontinence is on a psychosomatic basis. She should not have been subjected to surgery without a thorough psychiatric workup. We were a bit too optimistic.

### Summary and Conclusions

1. The anatomy of the female bladder, urethra, and associated structures is described.
2. The physiology of micturition is discussed.
3. Obstetric injury to the urethra and supporting structures is the commonest cause of stress incontinence.
4. Operations devised to correct stress incontinence are evaluated. All these procedures have in common the tightening of the fascial planes which surround the urethra, together with reduction of the urethral lumen.



adopted. As far as the future welfare of the mother is concerned, it is relatively unimportant how cleverly the accoucheur has manipulated the delivery, if he has neglected to carefully examine the genitals and repair any lacerations that may be present.

I do not advocate the universal adoption of puerperal gynecology by untrained men. The student, the practicing physician, and even the specialist must appreciate the difficulties as well as the advantages of this type of obstetric care and train toward perfection of technique as in any branch of major surgery. Our interns are given this training as part of their curriculum; judgment, speed, and dexterity are developed with experience so that even extensive repairs are accomplished at a minimum of risk.

There is another aspect of the subject that must be mentioned: this concerns ethics and the obligation of the physician and surgeon to give his patients the best possible care he can provide at minimal expense. I have heard that some obstetricians object to the principle of puerperal gynecology on the basis that it reduces their income; they are afraid of losing another fee for performing a subsequent gynecologic operation. Some obstetricians also raise the objection that they cannot devote the additional time for this service, especially during the night. My colleagues and I have often performed complete repair operations in the early hours of the morning, and we feel that the satisfaction of knowing that the required work has been done has more than compensated for the sleep thus lost.

During the first few years when the technique was in an experimental stage, the repair of old injuries was done about a week after delivery, and was called "the intermediary repair operation." With improved technique and judgment derived from experience, the time between delivery and repair was gradually shortened; finally, the operation immediately after delivery became routine (unless there were specific contraindications) and the term "immediate intermediary operation" was used. My first report of surgical repair of cervical lacerations performed immediately after expulsion of the placenta was published in 1918.<sup>1</sup> Up to 1930, a distinction was made between repair operations for old injuries and those performed for new ones. During the ensuing years, the procedures were called "gyneplastic repairs."<sup>5, 7, 10, 11</sup> Since 1931, I have used the term "puerperal gynecology"<sup>12-15</sup> to cover the whole field of repair of new, old, and combined injuries caused by childbirth.

The record of our cases over this long period are indisputable proof in refuting certain charges which have been made against the advisability of performing gyneplastic repair immediately after childbirth. It was formerly considered dangerous to invade the birth canal after delivery for fear of producing hemorrhage and of introducing infection. These can be avoided by careful technique and by observing the same aseptic and antiseptic precautions as in any major surgical operation. It has been claimed that the tissues are so edematous, bruised, and distorted that it is impossible to differentiate between temporary and permanent disturbances, and that many of these operations are unnecessary because there may be complete restitution after



## PUERPERAL GYNECOLOGY\*

### A Report of Thirty Years' Experience With Gyneplastic Repair Operations Immediately After Childbirth

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SINCE October, 1916, when I performed my first operation for repair of old lacerations of the genitals during the puerperal period, I have been advocating the value of repair of old, new, or combined injuries caused by childbirth, and, since 1918, I have presented numerous publications<sup>1-16</sup> on this subject. During the same period, other authors,<sup>17-33</sup> either as a result of my work or independently, have reported on operations performed during the puerperium for repair of old or new injuries. Nevertheless, the fact remains that the majority of obstetricians are still hesitant to do this work, and continue to regard such procedures as "too radical" and perhaps dangerous. Since the benefits accruing from this type of obstetric care are so great in terms of improved general health, greater working efficiency, economic saving, and probable protection from cancer in later life, I feel that it is important to restate the salient points of this work and to bring the record of my personal experience and those of my colleagues at Mt. Sinai Hospital up to date.

Progress cannot be made in any field unless so-called radical procedures are tried and evaluated; every innovation is considered radical until it is proved by long experience to be safe and practicable. Science is constantly producing startling changes in our environment and habits. That which was considered a radical surgical procedure a generation ago can now be done in comparative safety, because of improvements in surgical technique and hospital care. Certainly, the procedures that I am advocating, which I have practiced consistently for thirty years, and my colleagues for a slightly shorter period, may be said to have stood the test of time and to have long ago passed the experimental stage. Time has not changed, but rather has strengthened my conviction that puerperal gynecology is feasible, safe, and of immeasurable value to the patient and should be universally adopted as an integral part of natal care.

Since our results over thirty years show conclusively that the hazards of childbirth are not increased by immediate repair operations (provided no surgical contraindications are present), since the technique has been well standardized and has proved practical in the hands of various obstetricians, and since the health and comfort of the patients are so greatly improved by these methods, at enormous saving both to the patients and to the community, it is difficult to see why puerperal gynecology has not been more generally

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down from above and pulled down to the introitus from below with ring forceps without much force and with little trauma, due to the complete relaxation and stretching of the supporting ligaments of the uterus and the dilatation of the vaginal canal. Before beginning the repair, the uterine cavity is swabbed with gauze soaked in tincture of merthiolate solution, while further pressure is exerted on the fundus. This maneuver stimulates the uterus to further contraction, cleans out the blood clots, fragments of placenta or membranes, and helps to sterilize the uterine cavity, cervical canal, and vagina.

*Repair of the Cervix.*—This is the most important feature of puerperal operations. Rarely is an intact cervix found, even after a slow, normal labor. Any new lacerations, regardless of size, extent, and number are repaired. If a submucous tear is present, as evidenced by puckering or localized depression, a typical trachelorrhaphy is performed to reunite torn muscle fibers and the vaginal mucosa. In suturing the cervix, it is important that no pockets or fistulous tracts remain along the line of suture, that the vaginal mucosa on the outer side of the cervix is smooth, so that no adhesions may form between the cervix and the vaginal wall, that the external os is not so tightly closed as to interfere with drainage, and that no gaping occurs at the angles of the cervical os. If there is a pouching of the anterior cervical mucosa, owing to a submucous hemorrhage, the excess tissue is removed with an egg-shaped incision (endocervicectomy), the blood clot is evacuated, and the edges are brought together with a continuous interlocking suture of 00 chromic catgut. This requires only a few minutes and prevents subsequent pronounced endotrachelitis, which is a frequent cause of leucorrhea and subinvolution of the cervix and uterus.

*Cystocele.*—The degree of suffering resulting from a cystocele is unrelated to its size. Many patients with very slight bulging of the bladder suffer more than those who have pronounced herniation. A cystocele or an urethrocele is a hernia and cannot be cured without careful and complete mobilization of the involved tissues. When excessive tissue is allowed to remain, the patient complains of a fulness and irritation, even though the fascial and muscular structures are firm and in good position. It has been found at subsequent deliveries that the vaginal wall has sufficient elasticity to compensate for tissue that has been removed. The idea that a good perineal body will take care of a sagging anterior wall, i.e., a cystocele and urethrocele, is fallacious and without proof.

*Lacerations of the Vaginal Walls.*—Careful examination of the vaginal walls is carried out after repair of the cervix is completed. Deep structures are brought into normal position by the use of continuous or interrupted chromic sutures in one or more layers, depending on the depth of the laceration. All pockets must be eliminated. All severely traumatized, thrombosed, or ragged tissue is cut away, the parts are brought together, and the free edges of the mucosa are then united by a continuous, interlocking No. 1 chromic catgut suture.

*Rectocele.*—The object of the operation for repair of a rectocele is to remove the scar tissue, to cure the hernia, and to replace the various layers of muscle and fascia in their proper positions. A prophylactic rectocele operation may be performed on patients with no external evidence of perineal lacerations who present definite signs and symptoms of a rectocele. This condition may be recognized immediately after delivery by pouching of the rectum through the thinned or torn rectovaginal septum. This practically never returns to normal, but can be cured by exposing the fascia according to a previously described technique.<sup>14</sup> In repairing new perineal lacerations, episiotomies, or combined new and old tears, all severely traumatized, thrombotic, and scarred tissue is cut

childbirth. With experience, however, the lines of cleavage can be readily recognized and the various layers of tissues can be easily separated without tearing, and with less effort than in delayed gynecoplastic procedures. Any obstetrician who is also a gynecologist and has observed the end results of childbirth can prophesy in which cases the relaxation will be temporary and in which it will be permanent. It must be remembered that the degree of subsequent disability does not depend entirely upon the extent of relaxation or laceration. Hence, when future trouble is anticipated, a prophylactic repair of the cervix, a relaxed anterior vaginal wall (primary cystocele operation,<sup>6</sup> or the repair of a relaxed perineum immediately after delivery is much more effective and practical than a later operation to "cure" a serious disability.

It used to be said that the lochia would interfere with healing of tissues, but our experience, and that of many other surgeons, have disproved this contention. The lochia does not interfere with healing unless infection is present or the sutures are so tight as to obstruct circulation and cut through the tissues or interfere with drainage. Another objection has been that the patients are more comfortable during the lying-in period when repair operations are not performed. This is undoubtedly true, but since they are incapacitated at this time, anyway, the additional discomfort is willingly borne in the knowledge that another operation or prolonged disabilities are avoided.

It is not within the scope of this paper to repeat the indications, which are self-evident, or all the details of the technique used which I have already reported in numerous articles. Few changes have been made in our methods, except in the choice of analgesia and anesthesia. Recently we have been using demerol (100 mg.) and seconal (1.5 to 3 grains) routinely toward the end of the first stage of prolonged labor. When the patient is in active labor and the cervix is dilated at least two centimeters, the dose is repeated as often as necessary. We use nitrous oxide and oxygen, with or without ether, for the anesthetic in many deliveries and repairs as well as local, spinal, or sacral anesthesia, according to the preference of the operator and the indications in the individual case. Continuous caudal anesthesia has certain advantages, but has been used in only a small series of cases in our hospital because the care demanded has precluded its use during the war years. Recently we have used low lumbar anesthesia in a large proportion of cases. The infants cry spontaneously, bleeding is minimal, and the uterus remains contracted and firm after its use. The injection of anesthetic solution should not be begun before the cervix is dilated or severe cervical lacerations will occur. Nevertheless, even proper timing will not entirely prevent cervical lacerations; these will occur in some cases with any type of anesthesia or with any method of delivery.

A few important points in the technique must be stressed. Repair immediately after the delivery has many surgical advantages. One anesthesia serves for both delivery and operation. Danger of infection and its attendant morbidity are reduced. It has been proved that bacteria multiply in the uterus within two or three days after delivery: usually they are innocuous, but sometimes become pathogenic. Immediately after delivery, the cervix can be pushed

operations performed on the cervix and the 335 hemorrhoidectomies. Our records for the entire thirty years total over 20,000 operations.

Table V reports the complications that we encountered during this period. Although the morbidity following immediate gynecoplastic repair operations is somewhat greater than that following deliveries in which no operation is performed, this has not constituted a serious problem. With adequate measures to control infection, proper surgical technique, and use of modern methods to avoid dehydration, distention, anemia, and other conditions contributing to postoperative illness, the maternal morbidity has steadily decreased from 23.5 per cent in 1353 cases, 1922-1929 to 4 per cent in 10,254 patients delivered 1936 to 1946. In calculating the morbidity rate, the standard set by the American Congress on Puerperal Infection, any elevation to 100.4° F. or over on any two consecutive days, not including the first twenty-four hours after delivery, is used. This is a fallacious standard, for many women who have been badly lacerated and poorly repaired may not have any rise in temperature, but the morbidity is self-evident.

Our morbidity and mortality has been lower than that reported by institutions in which no gynecoplastic operations were performed during the puerperal period. In fact, since 1930, *there has not been one maternal death* that could possibly be attributed to a repair operation.

TABLE III. TYPES OF DELIVERIES

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	TOTAL
Prophylactic and low forceps	468	350	453	546	662	710	973	902	783	942	6,789
Midforceps	42	93	80	43	28	95	108	98	50	45	682
High forceps		6	2	4	1		2	2	1	3	21
Version and extraction	25	37	20	16	25	38	22	41	11	10	245
Cesarean section	30	25	26	33	36	34	49	48	36	61	378
Scanzoni maneuver	4	14	28	39	57	55	85	62	52	69	465
Manual rotation			2			11	3		15	22	53
Breech extraction	22	27	21	35	45	50	66	54	35	43	398
Piper forceps									7	4	11
Spontaneous	77	109	118	76	72	111	133	173	185	158	1,212
Total Deliveries	668	661	750	792	926	1,104	1,441	1,380	1,175	1,357	10,254

TABLE IV. TYPES OF OPERATIONS

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	TOTAL
Episiotomy	470	441	547	590	674	734	1,231	934	908	911	7,440
Trachelorrhaphy	265	225	232	211	195	223	226	265	151	200	2,191
Perineorrhaphy	82	39	99	102	100	90	85	122	31	85	835
Repair of perineal lacerations	40	80	47	34	31	45	42	56	98	79	552
Repair of vault lacerations		54	73	20	38	37	35	31	12	28	328
Cystocele		4			1	14	16	20	1	4	60
Cysto-Urethrocele	7		18	11	2	4	6	2			50
Rectocele		14	27	10	5	16	14	12			98
Hemorrhoidectomy	48	52	51	46	38	35	26	39			335
Endocervicectomy	3	6	7	2		3		2			23
Amputation of cervix	14	9	3	8	7	5	3	4			53
Dührssen's incision	12	15	12	16	14	25	26	12	11	8	151
Miscellaneous	5	3	9	19	10	60	20	37	14	24	201
Total operations	946	942	1,125	1,069	1,115	1,291	1,730	1,534	1,226	1,339	12,317

away, the various anatomic structures are identified and sutured in layers as for the repair of a rectocele. Any old relaxations or lacerations of the perineum are thoroughly exposed and treated, regardless of primary tears.

*Hemorrhoids.*—If any edematous or enlarged hemorrhoids are present, the sphincter ani is dilated and the hemorrhoids are either incised and the blood clots expelled, or the hemorrhoidal area is removed, followed by suture with No. 00 chromic catgut. In many instances, clusters of hemorrhoids have been removed by a modified Whitehead operation, with excellent results.

The obstetric activity at Mt. Sinai Hospital for the last ten years is demonstrated in the accompanying tables which supplement those in my previous reports and bring our records of thirty years' experience with puerperal gynecology up to date. Table I shows the age of the mothers delivered between 1936 and 1946. Contrary to popular belief, there was not a greater proportion of younger mothers during the war years. In fact, the 30- to 39-year group show the greatest relative increase. There is great satisfaction in the knowledge that complete restitution of lacerated genital organs in the very young women has spared them many years of possible invalidism.

TABLE I. AGE

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	Total
Under 20	22	17	21	24	18	13	35	58	49	55	312
20-29	465	398	498	529	615	753	908	876	724	869	6,725
30-39	175	233	224	231	282	326	392	428	392	417	3,100
40-49	6	13	7	8	11	12	16	18	10	16	117
Total	668	661	750	792	926	1,104	1,441	1,380	1,175	1,357	10,254

TABLE II. PARITY

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	Total
i	359	380	417	425	530	665	870	772	539	680	5,637
ii	195	183	226	250	296	312	436	467	421	488	3,274
iii	73	66	72	85	71	100	92	105	149	135	948
iv	29	22	20	17	19	17	31	28	34	45	262
v	5	4	4	7	5	7	5	4	19	4	64
vi	2	3	3	5	2	1	1	2	6	4	29
vii	2	2	2	1	1		4	1	5	1	19
viii		1	3	1	1	1	2	1	1		11
ix	1		1	1	1						4
x	1		1								2
xi			1			1			1		3
xii	1										1
Total	668	661	750	792	926	1,104	1,441	1,380	1,175	1,357	10,254

Table II indicates that there is a predominance of primiparas, almost twice as many as secundiparas, and six times the number of tertiparas. That repair operations should be delayed until the childbearing period is passed is thus proved impractical, since so many women limit their family to one or two children. Since 1920, the performance of immediate repair operations has become almost a routine practice by our obstetric staff, and the number of repair for old injuries has therefore constantly decreased. When multiparas return for subsequent deliveries, the old scar tissue is cut away immediately after delivery and current injuries are repaired, as in the cases of primiparas.

Table III charts the types of deliveries which totaled 10,254 from 1936 to 1946. The number of maternity cases has increased with a corresponding increase in the number of gynecologic operations.

Episiotomies have been listed in Table IV with the types of operations because they include a repair procedure. Of special interest are the 2,191

Others who have reported some type of gynecoplastic operations include Emge,<sup>17</sup> Kelly,<sup>18</sup> McCarley,<sup>21</sup> Emrich,<sup>22</sup> Hanna,<sup>23</sup> Speidel,<sup>25</sup> Macfarlane and Howe,<sup>26</sup> Traey,<sup>27</sup> Goff,<sup>28</sup> Christ,<sup>29</sup> Gayden and Plass,<sup>15, 30</sup> Bernstein,<sup>32</sup> and Guttmann,<sup>33</sup> and Hirst.<sup>34</sup>

The literature during the last few years has neglected this subject. Although some articles may have been overlooked because of obscure titles, a search of the *Index Medicus* failed to elicit any special reports of this work by other authors since 1937. It is discouraging to find, also, that numerous papers on progress in obstetrics<sup>35-40</sup> omitted mention of these procedures in modern obstetric care. Since the results in our hands have been so eminently satisfactory, and the advantages so obvious, it is indeed difficult to see why so many remain indifferent to this type of puerperal care, or refuse to acquire the necessary skill to practice it.

### Summary and Conclusions

A personal experience extending over thirty years in performing repair operations for new, old, or combined birth injuries immediately after the delivery is presented, along with additional statistical reports of puerperal gynecology as practiced in the obstetric department of Mt. Sinai Hospital from 1936 to 1946.

The importance of repair of cervical lacerations is stressed, and the salient features of the surgical technique are reviewed.

Our experience with thousands of operations performed immediately after delivery in a series of over 20,000 obstetric cases refutes all possible objections to these procedures. Although these operations require special training, skill, and care, they have proved successful in the hands of many different surgeons.

Advantages to the mother include improved general health, saving of time and money, prophylaxis against subsequent disabilities, and probable protection from cancer in later life.

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TABLE V. COMPLICATIONS FOLLOWING DELIVERIES AND REPAIRS\*

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	TOTAL
Fever of undetermined origin	2	11	2	4	15	18	16	20	2	10	100
Bronchitis	3	1			1		1				6
Pleurisy	1		1		1						3
Pneumonia	2	1		3		2	1			1	9
Retention of urine	4		1					1			6
Phlebitis	1				4	1		2			8
Thrombophlebitis		1		6	1	4	5	1	1	4	23
Perineal separation	6					2	1	1			10
Cystitis	12	8	13	10	10	12	18	16	15	19	133
Cystopyelitis	2	6	1	4	1	5	6	4	3	3	35
Shock	4		1								5
Transfusion reaction	6		1	1	1	3		1			13
Retained secundines		8	2			1		4	2	5	22
Atelectasis		1	1		1	2	3	2	4	3	17
Wound infection		1		1	2	2			3	2	11
Endometritis			4	14	10	17	16	6	2	3	40
Pelvic infection			1	1			2	1	4		9
Parotitis						1	1				2
Gastroenteritis			1				1				2
Inverted uterus									2		2
Postpartum hemorrhage			1				1		4	9	15
Total	43	38	30	44	47	70	71	60	42	59	504

\*Cesareans omitted.

*Duration of Hospitalization.*—In earlier years, most of the patients left the hospital by the fourteenth to the sixteenth day. This was later cut to about twelve days. During the last few years, when hospital facilities have been so strained, the time has been greatly reduced, and most of the mothers now leave the hospital on the fifth day, as is customary in other hospitals in which puerperal operations are not performed. So far, we have not found that there is any injurious effect on the mothers in thus shortening their stay in the hospital.

### Discussion

Although repair of new lacerations of the cervix had been reported many years earlier<sup>27, 28</sup> and had been widely practiced, the procedure had been largely abandoned in 1918, when I presented my first report on this subject.<sup>1</sup> I was not aware that this had been done previously when I began the practice of repairing old injuries during the puerperal period, and certainly the teachings of that time were all against it. As I have reported in another publication,<sup>12</sup> I later learned that Stuart and Hussey had described some work of this type in 1906 and 1916. DeLee told me that he had attempted such repairs in 1898, but later abandoned them.

During the period that my colleagues and I have been performing operations for new, old, and combined lacerations immediately after delivery, numerous authors have reported cases of this type, though most of them do not carry out the work on the extensive scale that we have done. The majority of the publications deal with repair of primary lacerations, though some include old lesions, particularly of the perineum.

In previous reports, I have mentioned the work of Polak,<sup>11, 15</sup> Pride,<sup>11, 12, 21</sup> Potter,<sup>11, 12, 19</sup> Sellers and Sanders<sup>24</sup> and Bailey, Toombes, Reinberger, Titus, Rongy, and Farrar, Friedlaender, Rothman, Kirshbaum, Bland, Boys, Williams, Holloway, Royston, Beardsley, Macdonald, Ristine, Wilson,<sup>12</sup> and Culbertson.<sup>16</sup>

## CONSTRICTION RING DYSTOCIA\*

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THE transverse extra or the intrauterine constriction ring complicating the first and second stage of labor still remains a serious problem. A review of 56 parturients, of which 54 were managed by qualified obstetricians, clearly demonstrates the necessity of further evaluating our management to improve the maternal and fetal mortality. The operative incidence in this series was 52, or 93 per cent, with two maternal deaths, or 3.5 per cent, and 18 fetal deaths, or 32 per cent. Failed vaginal operations occurred in 22, or 40 per cent, with a fetal mortality of 9, or 41 per cent. The types of constriction ring dystocia consist of: (1) the internal constriction ring and a potential prolonged first stage labor; (2) an external constriction ring complicating a potential prolonged first and second stage labor; (3) an internal constriction ring complicating the second stage labor. Our experience of this complication leads us to the conclusion that the management should be either one of ultraconservatism or a possible cesarean section. This should be based on the time the diagnosis is made during the first and second stage of labor.

We collected a series of 56 parturients from the Cook County Hospital, obstetric colleagues, and our private practices. Two were seen in consultation, while the balance were managed by qualified obstetricians.

The data of the series is as follows:

1. Mortality:
  - a. Gross maternal mortality of 2, or 3.5 per cent
  - b. Gross fetal mortality of 18, or 32 per cent
2. Parity:
  - a. Primiparas—27, or 48 per cent
  - b. Multiparas—29, or 52 per cent
3. Diagnosis was made:
  - a. First stage in 36, or 64 per cent
  - b. Second stage in 20, or 36 per cent
4. Gross operative incidence in 52, or 93 per cent
  - a. Fetal mortality of 16, or 30 per cent
5. Failed vaginal operations in 22, or 40 per cent
  - a. Fetal mortality of 9, or 41 per cent
6. Dührssen's incisions and forceps operation in 4, or 0.7 per cent
  - a. Fetal mortality of 1, or 25 per cent
  - b. Complications:
    1. Failed forceps in one which was followed by a craniotomy
    2. Shock in 3, one with severe sepsis
7. Diagnosis of the rings:
  - a. External in 21, or 38 per cent
  - b. Internal in 35, or 62 per cent

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sion, furrow, or ring of the uterus at various levels, seen or palpated on the anterior abdominal wall is significant. During cesarean section we have seen and palpated these rings and found them to correspond with an internal ring at the same site. We have 14, or 67 per cent, parturients who had these rings early in labor from thirty-six to eighty-eight hours when operative procedures were undertaken to terminate the labor. This external depression or furrow (we refer to it as a ring) is diagnostic of an internal constriction ring which in our opinion is pathognomonic.

*Type 3.*—Internal constriction ring complicating the second stage of labor. The usual procedure in a forceps operation is palpation of the cervix for the dilatation, application of the blades to the fetal head, and traction. In a version operation, the usual procedure is to palpate the cervix for the dilatation and the upward displacement of the fetal head out of the pelvic cavity, and to grasp one or two feet and complete the turning of the child. When these procedures fail, an intrauterine examination is made to determine the cause of the difficulty. If a ring is in the region of the fetal neck, the examining hand can usually reach it without much displacement of the fetal head and with slight danger of prolapse of the cord, but when the ring is much higher the fetal head must be displaced out of the pelvic cavity with great danger of prolapse of the cord. When the ring is in the region of the fetal neck, it is from 6 to 10 cm. from the external os.

### Treatment

The senior author in 1935 advocated a conservative management of the constriction ring dystocia of the first and second stage of labor which was based on his experience of 21 parturients and 350 parturients collected from the literature. A brief summary of his series will be presented: (1) gross maternal mortality of 54, or 15 per cent; (2) gross fetal mortality of 172, or 46 per cent; (3) external constriction rings of 24, or 9 per cent; (4) operative interference in 366, or 99 per cent; (5) failed vaginal operations in 154, or 42 per cent, of which 96, or 70 per cent, were failed forceps operations, with a maternal mortality of 26, or 27 per cent, and a fetal mortality of 27, or 33 per cent; (6) cesarean sections of 87, or 23 per cent, with a maternal mortality of 29, or 33 per cent, and a fetal mortality of 27, or 31 per cent. The experience gained from the above series and the present one has led us to adopt the management of first, ultraconservatism, and second, cesarean section which is based on the time the diagnosis of the constriction ring is made (Table I).

*Conservative Management.*—The basic principle involved is the maintenance of the parturient's mental and physical condition, and the prevention of maternal exhaustion during prolonged first and second stages of labor. It begins after eighteen hours of the first stage when the diagnosis is made of a potential prolonged first stage. The medical regime of maternal exhaustion is calculated for each twenty-four hours of labor. The urine is tested for acetone every twelve hours. A negative acetone test indicates that the parturient is being properly fed to prevent inanition and dehydration. The diet, liquid or soft, should consist of 3,000 calories of food rich in carbohydrates, and at least 2,000 c.c. of water for each twenty-four hours. This is best given in four-hour periods after an eight-hour period of consciousness which is used for feedings. Intermittent periods of sedation should be given to bring about the four-hour periods of rest or sleep. This regime is continued until the second stage is reached when the conditions present will determine the indication for delivery.

The ultraconservative management of constriction ring dystocia is to await the second stage until the ring has relaxed. This is determined by a further descent of the presenting part from its previous station. This will prevent hasty operative interference and failed operations in the second stage (Table II).

8. Location of the rings:

- a. Region of the "obstetric" internal os in 40, or 71 per cent
- b. Junction of the upper and lower uterine segment in 9, or 16 per cent
- c. In the upper uterine segment in 7, or 13 per cent

9. Delivery:

- a. Vaginal in 42, or 75 per cent
- b. Cesarean sections in 14, or 25 per cent (one a Porro cesarean section)
  1. First stage in 12, or 88 per cent
    - a. Maternal mortality 1, or 8 per cent
    - b. Fetal mortality, 0
  2. Second stage in 2, or 14 per cent (one a Porro cesarean section)
    - a. Maternal mortality, 0
    - b. Fetal mortality, 0

*Diagnosis.*—The cardinal criteria of the diagnosis of the complicating constriction ring of the first and second stage of labor remain the same as those given by the senior author in 1935,<sup>1</sup> except for the added importance of the transverse extrauterine constriction ring. They will be briefly reviewed. The diagnosis is speculative or absolute. The speculative diagnosis is a prolonged first stage, irregular uterine contractions, prolonged and intermittent periods of cervical dilatation, and the arrest of the presenting part in the second stage of labor.

The absolute diagnosis is the intrauterine palpation of a constriction ring, the state of the cervix and lower pole of the uterus, and a transverse extrauterine constriction ring. The signs and symptoms are as follows:

1. The uterine contractions vary in frequency, intensity, and duration. They may be of such a severe colicky nature as to cause the parturient to hold her abdomen with her hands with each contraction. Phillips<sup>2</sup> has called attention to these colicky uterine contractions in which the pain persists to and beyond the cessation of the contraction.

2. The station of the fetal head is stationary during the second stage.

3. The fetal head is loose in the pelvic cavity during uterine contraction which is pathognomonic.

4. The laxity of the cervix during the height of a uterine contraction. This is characteristic in that the cervix and the lower pole of the uterus are flaccid during the height of a uterine contraction. The external os does not contract or is not taut as it is during a normal uterine contraction, and is dilatable. When the cervical dilatation reaches 5 to 7 cm., the whole hand can easily be passed into the uterine cavity. This laxity is pathognomonic.

Mechanical dystocia (cephalopelvic disproportion, malposition, malpresentation, and pelvic and uterine neoplasm) should be ruled out during the prenatal supervision and shortly after the onset of labor for the management of a complicating constriction ring. This dystocia is not an active nor a predisposing factor.

The types of constriction ring dystocia may be stated as follows:

*Type 1.*—Internal constriction ring and a potential prolonged first stage labor. After eighteen hours of labor, the character of the uterine contractions and cervical dilatation (usually arrested for some hours) will indicate a prolonged first stage. The speculative diagnosis is a constriction ring dystocia. The absolute diagnosis is made by a sterile vaginal examination. The cardinal signs of the cervix and lower pole of the uterus is diagnostic.

*Type 2.*—External constriction ring and a potential prolonged first and second stage labor. The early appearance of a transverse extrauterine depres-

while the second stage parturients were treated by the ultraconservative management in 7, or 44 per cent, with a fetal mortality of 1, or 14 per cent.

This type will be summarized:

*Maternal death:* A para ii, in labor fourteen hours when seen by the senior author in consultation, ten hours after being admitted to the hospital. The parturient was in good condition, but she was apprehensive. The fetal heart tones were 140 and good quality. The cervical lips protruded from the vulva, and were succulent. The hand was easily passed into the uterine cavity to find a mento left transverse position at station minus 3, and a rigid ring around the head and above the pelvic inlet. The distance from the constriction ring to the external os was about 16 cm. Diagnosis was mento left transverse position and constriction ring dystocia. A number of vaginal and intrauterine examinations were made before she had been seen. A conservative management was suggested and followed. The parturient was seen twenty-six hours later, and the above findings were still present, but she showed the effects of the labor. The fetal heart tones were still 140 and good quality. A Porro cesarean section was performed. A live child was delivered. After the supracervical hysterectomy was done, it was seen that venous blood was oozing from the anterior wall of the cervical stump. This venous hemorrhage was controlled with difficulty after blood loss of approximately 800 c.c. Blood plasma was started in the operating room, and whole blood was to be given when the patient reached her room. She left the operating room with a blood pressure of 110/70, pulse of 90 and good quality, and appeared to be in good postoperative condition. Shortly after reaching her room the parturient became irrational, so that it was impossible to transfuse her with the whole blood. She became dyspneic and cyanotic, and died within two hours after leaving the operating room. The cause of death appeared to be due to secondary hemorrhage from the cervical stump and shock.

Summary of the management of this type:

1. First stage. Cesarean section followed by maternal death (as above).
2. Ultraconservative management in eight with one fetal death.
3. First stage. Manual dilatation and forceps:
  - a. Successful with mother in shock and child alive.
  - b. Failed, which was followed by ultraconservatism with good results to mother and child.
4. First stage. Version and extraction in two with two fetal deaths.
5. First stage. Nine centimeters fetal distress, Seanzoni midforceps with fetal death.
6. First stage. Dührssen's incisions and forceps in two.
  - a. Mother in shock and child alive.
  - b. Failed operation followed by ultraconservative management and a fetal death.

*Type 2.*—External constriction ring and a prolonged first and second stage labor. The senior author in his series of 1935 found 24, or 9 per cent, external constriction rings complicating the first and second stage, and did not appreciate its diagnostic importance. In recent years we have found that this ring is frequently present and persists with prolonged labors. In this series we have eight instances of prolonged first and second stage labors in which the ring persisted, which were managed by cesarean section. We have learned that the degree of the spasmodic contraction and the persistence of the external constriction ring, signs of the cervix and the lower pole of the uterus, and the character of the uterine contractions indicate a speculative duration of a labor. In an external constriction ring with a prolonged first stage, we determine the man-

TABLE I. COMPARISON OF THE TWO SERIES

	1935	1946
Total parturients	371	56
Gross maternal mortality	54, or 15%	2, or 3.5%
Gross fetal mortality	172, or 46%	18, or 32%
Operative interferences	366, or 99%	52, or 93%
First stage interferences	81, or 25%	24, or 43%
1. Maternal mortality	10, or 13%	1, or 4%
2. Fetal mortality	44, or 56%	9, or 37%
External constriction rings	24, or 9%	24, or 38%
Failed vaginal operations	154, or 42%	22, or 40%
1. Maternal mortality	48, or 31%	0
2. Fetal mortality	123, or 80%	9, or 41%
Failed forceps operations	96, or 70%	13, or 59%
1. Maternal mortality	26, or 27%	0
2. Fetal mortality	66, or 69%	2, or 16%
Cesarean sections	87, or 23%	14, or 25%
1. Maternal mortality	29, or 33%	1, or 7%
2. Fetal mortality	27, or 31%	0
Version, and version and extraction	142, or 38%	4, or 7%
1. Maternal mortality	26, or 18%	0
2. Fetal mortality	81, or 57%	3, or 75%

TABLE II. FAILED VAGINAL OPERATIONS IN 22, OR 40 PER CENT. FETAL MORTALITY OF 9, OR 41 PER CENT

FAILED VAGINAL OPERATIONS	FINAL METHOD OF DELIVERY										FETAL MORTALITY
	NO.	PER CENT	FORCEPS	VERSION	EXTRACTION	SECTION	DÜHRSSSEN AND FORCEPS	CRANIOTOMY	DELAYED FORCEPS	DELAYED SPONTANEOUS	
Forceps	13	59		1		1	1		9		2
Version	3	14	2	1							3
Forceps and version	1	4.5				Porro					0
Dührssen and forceps	1	4.5						1			1
Extraction*	2	9			2						2
Craniotomy	1	4.5						1			1
Bag	1					1					0

\*Breeches.

The management will be described under each type of constriction ring.

*Type 1.*—Management of an internal constriction ring and a potential prolonged first stage of labor. When the first stage is unduly prolonged, we speculate that the underlying cause is a constriction ring. After eighteen hours of labor, a sterile vaginal examination is made to determine the presence of the cardinal criteria of a constriction ring. If the diagnosis is a constriction ring, the management resolves itself to either the ultraconservative, or a possible cesarean section. The signs disclosed by the vaginal examination lead us to speculate on the probable duration of the labor. If we prognosticate that the labor will be unduly prolonged, the cesarean section may be elected, after a further functional test of labor of not more than ten hours to carry out this indication. There is no doubt that we erred in some instances, but we have learned from experience that in some cases that had labored forty or more hours, we wished in the retrospect that we had been more radical.

In this series we have 16, or 29 per cent, who were treated by a partial conservative management with one maternal death, or 9 per cent, and five fetal deaths, or 31 per cent. We note in this type vaginal operative interference in the first stage of 9, or 56 per cent, with a fetal mortality of 4, or 44 per cent.

Failed operations occurred in 16 or 84 per cent, with a fetal mortality of 5, or 31 per cent. The ultraconservative management was followed in 12, or 63 per cent, and a fetal mortality of 4, or 33 per cent.

Summary of this type:

1. Failed forceps followed by a low cervical cesarean section.
2. Failed forceps operation followed by a Porro cesarean section on account of a prolonged labor and potential uterine infection.
3. A failed Dührssen's incisions and forceps in the first stage followed by craniotomy in the second stage.
4. Two failed breech extractions caused by a ring around the hips which, after relaxation of the rings, were followed by extraction with two stillborn infants.
5. Vertex, with a difficult forceps delivery caused by the constriction of the external os around the fetal neck. The child was stillborn.
6. Vertexes, eight, failed forceps operation caused by rings about the fetal neck. Ultraconservative management was followed in five to thirteen hours with good results.
7. Vertex, a difficult midforceps caused by a ring around the neck. Traction continued with the delivery of a stillborn infant.
8. Vertex, child died early in the first stage. In second stage a failed craniotomy occurred. Conservative management for six hours and stillborn infant delivered by cranioclast.
9. Vertex, failed forceps occurred. Adrenalin given, ring relaxed, and the forceps operation completed with good results.
10. Vertex, failed forceps occurred, and during the operation the cord prolapsed. Traction continued with the delivery of a stillborn infant.
11. Vertex, failed forceps occurred. The ring was around the neck. Adrenalin was given and the ring relaxed. A version and extraction was accomplished with a stillborn infant.

### Discussion

Since Smellie in 1730<sup>3</sup> described an internal constriction ring as a "navel string," 22 different terminologies have been applied to this complication of labor. The various current names are the ring of Bandl, contraction of the ring of Bandl, contraction ring dystocia of White,<sup>4</sup> retraction ring dystocia of Pride,<sup>5</sup> simply contraction or retraction ring, uterine contraction rings, and constriction ring of Rudolph.<sup>1</sup> Rudolph maintains that the ring occurs at various levels of the parturient uterus, i.e., in the upper uterine segment, junction of the upper and lower uterine segments, at the "obstetric" internal os, ring of Muller, or the true internal os of Schroeder,<sup>6</sup> and the external os. Be as it may, the fact remains that it is becoming an established clinical entity by whatever name the complicating ring is designated. This clinical entity is as yet not well established in the diagnosis and management which necessitates our interest.

A review of this series demonstrates that the high operative incident, failed vaginal operations, fetal mortality, and the potential maternal mortality demands a careful consideration of the management of constriction ring dystocia. A comparison with the senior author's series of 1935 again demonstrates that our present series need to be evaluated.

agement after eighteen hours of labor. With or without a sterile vaginal examination we will treat the patient conservatively, and after about ten hours more decide the management of either the ultraconservative or cesarean section. We believe that cesarean section is hazardous late in the first or in the second stage of prolonged labors. We note in this series we have eight cesarean sections which were performed after a labor of thirty-six to eighty-eight hours with good results. We have performed three cesareans after a labor of sixteen to twenty-four hours with good results. This may appear radical, but our experience with prolonged labors has demonstrated that the abdominal operation should be performed early, when the conditions are favorable, rather than late when the conditions are not favorable.

In this series we have 21 or 38 per cent external constriction rings present early in labor. The maternal mortality was one, or 5 per cent, and the fetal mortality was 3, or 14 per cent. Cesarean sections were performed in 12 parturients after a labor of thirty-six to eighty-eight hours with no maternal or fetal mortality. Vaginal delivery was done in nine parturients with a fetal mortality of 4, or 44 per cent. This type will be summarized to indicate the conditions and indications.

Summary of the management of this type:

1. Ring present when the second stage was reached. A difficult midforceps with the death of mother and child during the extraction.

2. Cesarean sections in 12 (hours of labor, one group of 36, 55, 56, 60, 48, 88 and 54: second group of 18, 20, 22 and 24 hours) with good results to mother and child.

3. Ultraconservative management in five parturients with a fetal mortality of one.

4. First stage, 9 cm., difficult version with the delivery of a live child; rupture of the uterus with the placenta in the abdominal cavity which was followed by a supracervical hysterectomy.

5. Dührssen's incisions and forceps in one with a live child; mother in severe shock and sepsis who recovered.

6. Conservative management to the second stage with the ring present. Failed low forceps on account of the ring around the neck. Some hours later a craniotomy was done.

*Type 3.*—Internal constriction ring complicating the second stage of labor. When an operative procedure is contemplated in the second stage after a prolonged first stage, a persistent station of the presenting part and the character of the uterine contractions should be speculative of a constriction ring dystocia, while an external constriction ring persisting is an absolute diagnosis of this dystocia. At this stage the cervical lips are retracted to or above the widest diameter of the presenting part. In the routine application of most forceps operations the absolute signs of a complicating ring are easily missed. Therefore, when the second stage is reached, the forceps or version operation is a trial procedure. When difficulty arises in an operative procedure, an intrauterine diagnosis is made to account for the apparent failure of the operation. Excessive traction should be avoided in a forceps operation when resistance is met in attempting to pull the fetal head out of the pelvis. When the diagnosis of a constriction ring is made, the ultraconservative management is instituted until the ring relaxes. This is recognized by the presenting part descending to a lower station. This is a presumptive sign that the ring has relaxed, but it may appear again during the operative procedure.

In this series we have 19, or 34 per cent, parturients who reached the second stage with no maternal mortality, and a fetal mortality of 8, or 42 per cent.

nose the complication early and to prognosticate the probable duration of the labor, then only does the cesarean section become an indication to be considered. We believe that after eighteen hours of the first stage, a vaginal and an intra-uterine examination for the cardinal criteria of constriction ring dystocia, or the presence of the external constriction ring will aid us in determining the indication for delivery. After waiting ten hours more we can decide definitely our management which is either ultraconservative or cesarean section for the safety of the parturient. The study of the series of 1935 and 1946 demonstrates that vaginal operative procedure must be carefully evaluated for constriction ring dystocia.

### Conclusions

1. We have presented 56 parturients with a constriction ring dystocia.
2. The maternal mortality is 2, or 3.5 per cent, and a fetal mortality is 18, or 32 per cent.
3. The operative incident is 2, or 93 per cent, and the failed vaginal operations are 22, or 40 per cent.
4. The operations of Dührssen's incisions and forceps, manual dilatation of the cervix, and version and extraction are mentioned only to be condemned for constriction ring dystocia.
5. The ultraconservative management, and cesarean section when properly evaluated are the methods advocated by the authors.

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The appreciation of the diagnostic significance of the external constriction ring in 21, or 38 per cent, parturients in this series has been the outstanding clinical sign to aid us in the management of this complication. Its early presence in labor, and its persistence in labor have indicated to us a potential prolonged labor, and its presence contraindicates vaginal operative procedures. We recognize that the prolonged first stage of labor is still a trying one in its management. It is well known that the ultraconservative management of a protracted labor invites a fetal mortality of about 10 per cent, and a slight danger to the parturient.

Some of the vaginal operative procedures in this series will be described in order to condemn them: (1) four Dührssen's incisions and forceps with one fetal death, one failed procedure which was followed by craniotomy, and resulting shock in all parturients after the delivery, and one parturient with a severe sepsis; (2) two manual dilatation of the cervix and forceps with one fetal death, one failed and then treated by the ultraconservative management with good results, and one parturient had mild shock after the delivery of the stillborn infant; (3) version, or version and extraction, four with three fetal deaths and one version and extraction with nine centimeters cervical dilatation with a live child delivered, but rupture of the uterus which was followed by a supracervical hysterectomy with good results to the parturient. These procedures appear to be relics of accouchement forcé.

The maternal deaths will be discussed: (1) The parturient seen by the senior author is unique in that he has not found nor seen a similar instance of the protrusion of a marked passively congested cervix and the lower pole of the uterus from the constriction ring. It was forty hours from the onset of labor when the Porro cesarean section was decided upon and performed. This death is left open for discussion. (2) A death from a midforceps operation when the external constriction ring was present. The parturient was in labor forty hours when the second stage was reached. The ring was present when the forceps operation was begun. After great difficulty in descent of the presenting part, an intrauterine examination was made which disclosed a constriction ring around the fetal neck. The traction was continued with a stillborn infant delivered, and the death of the mother as the infant was delivering. We believe that this parturient should have been managed by the ultraconservative management, or, if the child was dead or in a poor condition, a craniotomy, providing the parturient was not in shock.

The ultraconservative management will be agreed upon for the prolonged first and second stage. The suggested cesarean section will bring up the question of its abuse. We still believe that the vaginal route is the safest for the parturient, but constriction ring dystocia complicated by prolonged labor and the potential dangers of vaginal delivery must be seriously considered. The prolonged labor is still a problem in its physiology and management, but in cesarean section reports from various clinics, this operation is performed in instances of prolonged labor. When one reviews the statistics of constriction ring dystocia, we must appreciate the danger to the parturient with this complication. When one becomes conscious of this entity, and has learned to diag-

In order that the study might be of statistical value, routine admissions to the obstetric floor for vaginal delivery were given this method of anesthesia, with few exceptions. Elective versions were excepted because of the absence of adequate uterine relaxation. A few cases of frank breech were excepted where we did not choose to lose the "bearing down reflex" and then have to do a Pinard maneuver on one or both legs. Multiparas previously delivered without episiotomy were excepted in most instances. All patients were carefully questioned for history of disorders that would, in themselves, be contraindications to the giving of a spinal anesthesia. Dislosure at physical examination of any disorder of the spinal column or central nervous system was also considered a contraindication.

When the method was first undertaken, there was a necessary trial of dosage. As much as 30 mg. and as little as 15 mg. of metycaïne were employed. After determining 22.5 mg. (1.5 c.c. of 1.5 per cent solution) to be the minimal practicable amount, we did not vary from this dose. This series includes 1,000 consecutive cases, with 1,008 deliveries, there being eight sets of twins. No cases having larger or smaller dosages are included in this report. These 1,000 patients all received 1.5 c.c. of a 1.5 per cent solution of metycaïne in Ringer's solution, specifically 22.5 mg. Our definition of "minimal dose spinal anesthesia" in obstetrics implies the intrathecal administration of the smallest amount of an anesthetic agent specifically placed which will obliterate uterine and perineal pain in delivery.

In "minimal dose spinal" one is using one-twentieth of the caudal dose, and there is little uncertainty as to its destination upon injection. The injection requires only a very few minutes and anesthesia follows almost immediately.

### Method

In this initial series the injection was made when the patient was ready for delivery, with few exceptions. In primiparas the cervix was completely dilated, and in most instances the head on the perineum; exceptions to the latter were instances wherein descent had ceased for a long enough time to warrant operative interference. Many multiparas were intentionally given their injections before complete dilatation. Anesthesia lasts about sixty to ninety minutes. One can anticipate completion of dilatation within that period of time in many instances of rapidly progressing labor and easily allow for delivery and episiotomy closure. Occasionally, rectal examinations were misinterpreted, and primiparas were given the injection before complete dilatation. In most of these instances also, dilatation was completed before the anesthesia "wore off." An occasional patient was given a second injection. Usually the injection was made with the patient on the delivery table; occasionally it was given in the labor room. With "minimal spinal," one does not sacrifice the patient's ability to cooperate in getting on and off the delivery table. She can usually move her legs, although there may be some adductor weakness. A blood pressure cuff is applied, and the Bell type stethoscope secured over the antecubital space. Long tubing permits placing the "Aneroid" and stethoscope headpiece by the patient's shoulder. This permits taking frequent readings without having to remove the arm from the fastened position at the patient's side. The left lateral position is generally employed; occasionally obese patients are placed in the sitting position. The skin

# MINIMAL SPINAL ANESTHESIA IN VAGINAL DELIVERY\*

## An Analysis of 1,000 Consecutive Cases

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**S**PINAL anesthesia has certain distinct advantages over all other forms of regional anesthesia. If spinal anesthesia can be used in the obstetric patient with the same degree of safety as in the nonpregnant, it deserves a place in the obstetrician's armamentarium. All forms of regional anesthesia are accepted as the safest for the baby for the obvious reason that they minimize the danger of neonatal apnea.

Perineal block, parasacral, and sacral block, ideal as they are for many deliveries, do not give uterine anesthesia, and are difficult of administration to the uncooperative patient. Terminal caudal is a regional anesthesia that does give both uterine and perineal anesthesia, but caudal anesthesia presents inherent technical difficulties and, in addition, the time factor often restricts its use. After insertion of the needle into the caudal canal, one must wait ten minutes after injection of a test dose to make certain the needle has not perforated the dura. The anesthetic dose is then injected, and about fifteen minutes thereafter anesthesia is achieved. Most anesthetic casualties in the use of caudal block have been due to the inadvertent intrathecal injection of the necessarily large quantity of drug used. The generally accepted initial test dose implies this ever constant danger.

Numerous reports on the use of spinal anesthesia in obstetrics have appeared since Pitkin and McCormack's<sup>1</sup> report in 1928. Recent examples are papers by Parmley and Adriani,<sup>2</sup> and Weaver, Adamson, and Johnson.<sup>3</sup>

Spinal anesthesia in obstetrics has been in disfavor because of fear of blood pressure fall and shock, the danger of uterine atony followed by hemorrhage, and the danger of intrathecal infection and/or toxic reaction and neurological sequelae. The latter danger, namely, infection and/or toxic reaction, is not limited to the obstetric patient and occurs rarely indeed, as shown by the widespread use and proved safety of spinal anesthesia in the various surgical specialties.

As obstetricians, it was our belief that if a small dose were used, and if it were specifically placed, satisfactory anesthesia, both uterine and perineal, could be achieved without impairment of uterine motor activity and without sufficient vascular relaxation to permit blood pressure fall and shock. Gratifying results initially so encouraged us that we proceeded with this study to acquire a series large enough to permit certain significant clinical conclusions as to its effect on the conduct of labor and on morbidity and mortality, both fetal and maternal.

\*Presented at the Fourteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Chicago, Ill., Sept. 19 to 21, 1946.

TABLE II. OPERATIVE PROCEDURES

	PRIMIPARAS	MULTIPARAS
Low forceps	545	187
Midforceps	22	6
Aftercoming head forceps	12	2
Internal version	2	1
Total	581	196

## Interpretation of anesthetic results:

- 1+ Very slight anesthesia effect
- 2+ Unsatisfactory anesthesia (often requiring supplemental anesthesia)
- 3+ Mild discomfort
- 4+ Complete anesthesia

A 2+ result (either uterine or perineal effect) was considered unsatisfactory, and in these cases supplemental anesthesia was often necessary to complete delivery or episiotomy closure. A few cases, completed without supplemental anesthesia, were listed as failures because of the magnitude of the patient's complaints, namely, painful uterine contractions or perineal pain on delivery of the baby.

A perineal anesthesia failure (2+ or less) occurred in 53 cases (5.3 per cent), of which 13 were complete failures (1.30 per cent) (Table III). Of the 53 cases, 51, or 5.10 per cent, of the total 1,000 cases required some form of supplemental anesthesia. Twenty-five, or 2.5 per cent, required supplemental ether anesthesia for delivery and 24, or 2.4 per cent, were given pudendal block. One was given nitrous oxide inhalation, and one given intravenous sodium pentothal, as shown in Table IV.

TABLE III. PERINEAL ANESTHESIA FAILURES

Partial	40	4.00%
Complete	13	1.30%
Total	53	5.30%

TABLE IV. SUPPLEMENTAL ANESTHESIA

Ether inhalation	25	2.50%
Perineal block	24	2.40%
Nitrous oxide inhalation	1	0.1 %
Intravenous sodium pentothal	1	0.1 %
Total	51	5.1 %

In this series of 1,000 cases there were three instances of complete failure to relieve discomfort from uterine contractions (0.3 per cent). There were 31, or 3.1 per cent, who had only partial relief of uterine pain (Table V). On a rare occasion, a patient reported discomfort referred to the lower abdomen when forceps traction was applied. This same type of discomfort was occasionally noted when an occiput posterior was being rotated to the anterior position.

As previously stated, blood pressures were taken before injection, and fifteen minutes and thirty minutes thereafter. The average drop in pressure

TABLE V. UTERINE ANESTHESIA FAILURES

Partial failure	31	3.10%
Complete failure	3	0.3 %
Total	34	3.4 %

is prepared with soap, ether, and tincture of merthiolate. After draping, the first lumbar interspace is found. This level is chosen advisedly as being anatomically and physiologically correct because pain fibers from the uterus enter the spinal canal at the level of the eleventh and twelfth thoracic nerves. It is our intention to block them as close as possible to their point of entry into the spinal canal rather than depend upon large dosage and dispersion of the anesthetic agent to reach this level.

Meteyaine 1.5 per cent in Ringer's solution is employed. After infiltration of the skin and subcutaneous tissues, using a 2 c.c. syringe of the same solution, a No. 22-gauge short beveled needle is inserted into the spinal canal. This small needle is used, hoping thereby to reduce to a minimum the subsequent trauma leakage of cerebrospinal fluid. A No. 20-gauge needle is also on the sterile tray and is used when the operator is unable to introduce the fine caliber needle into the spinal canal. After withdrawal of the stylette, and at the first appearance of a crystal clear "bead" at the needle's hub, 1.5 c.c. (22.5 mg.) of meteyaine is injected from a 5 c.c. syringe. The injection is made slowly, between uterine contractions, thereby minimizing dispersion. The patient is promptly turned on her back, and the head of the delivery table raised one foot, about 20 degrees. After ten minutes, the table is returned to the horizontal.

A 1.5 per cent solution of meteyaine is very slightly hyperbaric, and tends to seek a lower level. Within a few minutes, the sensory fibers of the second, third, and fourth sacral nerves are also anesthetized. These carry pain sensation from the cervix and lower birth canal. With this technique, anesthesia usually reaches a level between the umbilicus and the xyphoid. There is no obliteration of uterine motor activity. This function is thought to be controlled by fibers derived from the sixth thoracic segment. As previously stated, the patient can usually move her thighs, legs, feet, and toes. Immediately after the injection, the thighs are placed in stirrups, and preparations made for delivery in the usual manner. After the injection, the operator scrubs for ten minutes, and anesthesia is complete in fifteen minutes. The blood pressure is taken before the injection, and fifteen minutes and thirty minutes thereafter. An oxygen administration apparatus and the usual stimulants needed to combat vascular collapse are constantly kept in readiness.

Episiotomy followed by elective outlet forceps was practiced, but spontaneous delivery was encouraged when easy prompt outcome was anticipated. Many patients will bear down when told to do so, and, although the mechanism giving them the natural urge to push is obliterated, there is no paralysis of the abdominal muscles.

Of the 1,000 cases, there were 652 primiparas (65.20 per cent) and 348 multiparas (34.80 per cent). Of the total, 224, or 22.40 per cent, delivered spontaneously; 776, or 77.60 per cent, were operative deliveries. The operative incidence was 88.96 per cent in the primiparas and 56.32 per cent in the multiparas, as shown in Table I.

TABLE I. DELIVERY METHOD

	PRIMIPARAS		MULTIPARAS	
Spontaneous	72	11.04%	152	43.68%
Operative	580	88.96%	196	56.32%
Total	652	100.00%	348	100.00%

Operative procedures employed are shown in Table II.

### Results

Anesthetic results were tabulated, listing uterine and perineal anesthesia separately. Each was evaluated on the basis of 1, 2, 3, or 4 -. A 4+ was considered perfect anesthesia.

TABLE VII. PATIENTS WITH POSTPARTUM HEADACHE

Postspinal in origin	63	6.30%
Other causes established	9	0.90%
Total	72	7.20%

A review of Table VIII makes obvious the contention that this type of headache, when typical and definite, usually lasts through a week, and may persist longer. The more severe headaches usually persisted the longest. Our two cases of headache which lasted until the tenth postpartum day were the most severe in the entire thirty. No means, save repeated doses of codeine and the supine position, served to ameliorate this distress. In many of the mild cases of short duration we suspect that an element of suggestion plays a part. An occasional instance of lumbar backache or pain in the cervical region occurred. These were usually not associated with headache. In these latter instances, physiotherapy in the form of heat and massage offered quite prompt relief.

TABLE VIII. DURATION OF SPINAL HEADACHE

Subsided on the first day	0
Subsided on the second day	1
Subsided on the third day	4
Subsided on the fourth day	5
Subsided on the fifth day	8
Subsided on the sixth day	8
Subsided on the seventh day	2
Subsided on the eighth day	0
Subsided on the ninth day	0
Subsided on the tenth day	2
Total	30

With early ambulation (up on the second postpartum day), we believe the incidence of urinary retention has been kept to a minimum. Cases requiring catheterization two or more times in the postpartum period were classified as having urinary retention, and there were 15 cases encountered (1.5 per cent). Fourteen were primiparas and one was a multipara. Some obvious complication, such as traumatic delivery, infection, laceration, etc., was present to explain faulty bladder dynamics in all save three. In these three spinal anesthesia might have been a factor, but no proof exists as to the deleterious effect of the spinal in any of these cases.

There were no instances of infection at the site of injection, no meningeal infections, and no neurological sequelae.

There were 18 infant deaths, intrapartum or in the neonatal period (1.8 per cent), in this series. None of these deaths was attributable to the anesthesia, so the corrected fetal mortality was 0 per cent. Causes of death are listed in Table IX.

TABLE IX. UNCORRECTED INFANT MORTALITY

Prematurity	5
Congenital defect	5
Intrauterine death	2
Breech presentation (2nd twin)	1
Ablatio placenta	1
Placenta previa	1
Atelectasis	1
Pneumonia	1
Intracranial injury	1
Total	18 (1.80%)

in the entire series was 14 mg. Hg systolic, and 7 mm. Hg diastolic. There were no instances of shock in the entire series. Also, there were no instances of nausea attributable to the injection, as is so frequently seen following spinal anesthesia when larger doses are used. Many patients have no perceptible fall in either systolic or diastolic pressure. The greatest fall in pressure occurred in one patient whose blood pressure of 92/62 before injection suddenly dropped to 68/25, but at no time did she show any clinical symptoms of shock. She was promptly given ephedrine sulfate ( $\frac{3}{8}$  grain) intramuscularly and her pressure returned to its former level without incident.

Pulse changes in the entire series were checked carefully before and after injection. The physiologic bradycardia that normally follows delivery is apparently unaffected by an intrathecal anesthetic agent.

Although we have not been fortunate enough to determine blood loss accurately, a sincere effort was made in each instance to estimate it objectively. The average loss was very close to 100 c.c., definitely lower than blood loss encountered in cases where inhalation anesthesia was employed. A blood loss of over 500 c.c. was considered a postpartum hemorrhage. There were 11 instances so classified, or 1.10 per cent in 1,000 cases. Our impression is that minimal spinal anesthesia insures the same advantage in decreasing blood loss in the third stage of labor as has been quite generally accepted for caudal anesthesia. There was no instance of shock or sensitivity, as previously stated. All 11 postpartum hemorrhage cases responded without incident to the administration of intravenous ergotrate ( $\frac{1}{320}$  grain) and blood replacement therapy, namely, plasma or whole blood. Uterine atony was not demonstrable clinically in any of these 11 instances.

Our criteria for morbidity was a temperature of 100.4° F. occurring on two or more days, not including the day of delivery. There were 43 such morbid patients, or 4.30 per cent, as shown in Table VI.

TABLE VI. COMPLICATIONS OF FEBRILE (MORBID) PATIENTS

Puerperal infection (endometritis, etc.)	20	2.00%
Urinary tract infection	10	1.00%
Mastitis	4	0.40%
Infection of perineum, etc.	4	0.40%
Dermatitis venenata (merthiolate sensitivity)	1	0.10%
Respiratory infection	2	0.20%
Infusion reaction	1	0.10%
Cause unknown	1	0.10%
Total	43	4.30%

Headache was the most annoying complication of the postpartum period. There was a total of 72 patients with this complaint (7.2 per cent). This includes all patients who required codeine grain  $\frac{ss}$  on two or more occasions in an attempt to achieve relief. Inasmuch as headache is not uncommon after delivery, with labor, analgesia, anemia, fatigue, etc., playing a part, a postspinal headache was counted as such only in the absence of other obvious causes. Differentiation of causes was not possible in all cases, but there were nine instances (0.9 per cent) wherein there were other obvious causes for headache, such as toxemia, respiratory infection, etc. There then remained 63 instances, or a corrected incidence of 6.3 per cent, of the entire series wherein postpartum headaches seemed definitely postspinal in origin (Table VII). These varied in their duration, all having their origin in the first twenty-four to forty-eight hours, and lasting from one day to ten days.

Thirty of these 63 patients' charts revealed accurate data as to the day of subsidence of their postspinal headaches.

## THE MANAGEMENT OF DELIVERY FOLLOWING STILLBIRTH FROM PREVIOUS DYSTOCIA\*

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THE obstetric patient who becomes pregnant after having lost her first baby from dystocia presents a problem that should receive the serious attention of the obstetrician or the physician who manifests an especial interest in obstetrics. The success which attends the second delivery of such patients may be considered a measure of the justification of specialization or of special interest in obstetrics. Women who have lost their first-born from dystocia have undergone a trying experience and a bitter disappointment. This distressing result obtains in only rare instances in the modern practice of obstetrics. It is almost imperative that a normal baby be delivered in future pregnancies. Women who comprise this small group of obstetric patients should have every assurance that a normal, living infant will be born at subsequent deliveries, but at the same time no unnecessary maternal risk should be involved.

Because a review of the literature for the twenty years from 1916 to 1936 failed to reveal a specific reference to cases of this interesting group, Mussey and one of us (A. B. H.)<sup>1</sup> felt a report of a series of cases was needed. That report was presented to this society ten years ago and covered experience at the Mayo Clinic with 33 cases of this obstetric complication during the decade immediately preceding 1936. We now wish to augment that report by presenting an additional 32 cases observed in the Section on Obstetrics of the Mayo Clinic in the decade that has intervened.

In the period covered by the initial report (of 33 cases) there were 3,953 deliveries, or an incidence of one stillbirth from dystocia for every 120 deliveries (0.8 per cent). During the past decade in which there were 32 cases, there were 7,265 deliveries, an incidence of one such case for every 227 deliveries (0.4 per cent). It is encouraging that the percentage incidence of these cases has been reduced by nearly 50 per cent in ten years. This fact probably represents improvement in obstetric practice in the community. The wider application and more intelligent use of prenatal care and such relatively recent improvements as roentgenographic pelvimetry may play a role.

The data gathered ten years ago is shown in Table I, together with the uncorrected fetal mortality rate of 4 per cent and a corrected fetal mortality rate of 2 per cent in 50 deliveries subsequent to fetal death from dystocia in the primary pregnancies.

Our data concerning experience with the same type of cases in the last ten and one-half years from Jan. 1, 1936, to July 1, 1946, is given in Table II.

\*Read before the Fourteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Chicago, Ill., Sept. 19 to 21, 1946.



### Comment

Analysis of the results in these 1,000 vaginal deliveries conducted under minimal dose spinal anesthesia reveals no instance of the usually feared side effects of spinal anesthesia in the obstetric patient. The high incidence of outlet forceps delivery common to most regional anesthetic methods prevailed in this series also. The occurrence of postspinal headache in 6.3 per cent of the cases was the only undesirable subjective factor. The favorable effect on the baby plus the minimal trauma to the birth canal which can be achieved when such a high degree of perineal relaxation is attained suggests to us that this method of anesthesia for operative deliveries has many advantages over inhalation agents, and compares favorably with other regional anesthetic methods.

### Summary

1. One thousand cases delivered under "minimal dose spinal anesthesia" are reported. There were 1,008 deliveries, there being eight sets of twins.

2. Metyeaine, 22.5 mg. (1.5 c.c. of a 1.5 per cent solution), was found to be the minimal practical dose, and was used in every instance in this reported series.

3. Method of administration is described in detail.

4. Method of delivery and maternal morbidity is analyzed.

5. There were no instances of the usually feared side effects of spinal anesthesia in the obstetric patient.

6. "Minimal spinal anesthesia" in this series proved to be a safe and desirable anesthetic method for operative vaginal delivery, and the results indicate it deserves a place in the obstetrician's armamentarium for use in selected cases.

The opinions expressed herein are those of the writers and are not necessarily those of the Navy Department.

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often led to disastrous fetal results. Evidence suggested that there were several instances of premature operative intervention. Conversely, it seemed that perhaps some patients were allowed to labor too long for the good of the infant when conditions were favorable for a moderately easy operative delivery.

### Deliveries After Previous Stillbirths

We may state as was done in the paper on this subject presented ten years ago: "The method of delivery to be employed for parous women whose babies have previously been born dead makes an interesting study. As term approaches, a selection must be made of those patients for whom a test of labor may be tried. The fact that a woman has lost a baby from dystocia does not indicate, per se, that elective cesarean section must be employed routinely in subsequent deliveries." The method of delivery used in the series of cases from 1936 to 1946 is correlated with the type of pelvis in Table III. No single criterion should

TABLE III. TYPE OF PELVIS CORRELATED WITH METHOD OF DELIVERY

TYPE OF PELVIS OR PERTINENT DATA	NUM- BER	TYPE OF DELIVERY				DE- LIVERIES
		SPON- TANEOUS	OUTLET FORCEPS	MID- FORCEPS	CESAREAN SECTION	
Gynecoid with adequate measurements	16	15	1	1	2	19
Anthropoid	2	2				2
Platypelloid	3	1			2	3
Platypelloid, small gynecoid	2				3	3
Gynecoid convergent	2		2			2
Gynecoid; android	1	1				1
Small gynecoid	2				2	2
Anthropoid with convergent canal	1				1	1
Anthropoid with marked midplane contraction	1				1	1
Previous fractured pelvis at delivery elsewhere	1				1	1
Two breech deliveries with stillbirth associated with recurrent toxemia	1				1	1
Total	32	19	3	1	13	36

decide the method of delivery. If the pelvis is adequate and there is a normal vertex presentation, the prospects for successful delivery through the pelvis are excellent. The physician who delivers the patient subsequent to stillbirth from dystocia has the tremendous advantage of the fact that the cervix has been dilated previously. Uterine inertia and so-called soft part dystocia are unlikely to reappear as a formidable complication.

Thirteen elective cesarean sections were done in the series of 32 cases encountered in the last ten and one-half years. In nine of these, definite pelvic contraction was the indication for such delivery. One of the remaining cesarean sections was done because the patient had sustained a fractured pelvis and soft tissue trauma at her primary delivery elsewhere which had required extensive orthopedic and plastic surgery. Another cesarean section was performed in a case in which two stillbirths previously had been associated with breech deliveries and recurrent toxemia. The other two cesarean sections in the presence of an adequate pelvis require comment. These two operations involved the same patient, a woman weighing more than 250 pounds (113.4 kg.). She was first seen in 1936 for emergency treatment because of failure of attempts to deliver the aftercoming head of a large fetus (which weighed 4,900 Gm.). Intrapartum sepsis existed from which recovery followed. She subsequently reappeared on two occasions with ruptured membranes and shoulder presentations

TABLE I. FETAL MORTALITY IN CASES ENCOUNTERED FROM 1926 TO 1935, INCLUSIVE\*

	BABIES		FETAL MORTALITY, PER CENT
	LIVING	DEAD	
First delivery (at clinic or elsewhere)	0	33	100.0
Second delivery (elsewhere)	0	5	100.0
Next delivery (in five cases the third)	32	1	3.0
Subsequent deliveries	16	1	5.9
Total deliveries after first stillbirth	48	2	4.0
Corrected fetal mortality†		1	2.0†

\*Table with emendations from Hunt, A. B., and Mussey, R. D.: *AM. J. OBST. & GYN.* 34: 310-315, 1937.

†On basis of one fetal death in 50 deliveries subsequent to stillbirth, the other infant dying of a congenital anomaly and urinary infection eighteen days after cesarean section.

TABLE II. FETAL MORTALITY IN SECOND SERIES (1936 TO JULY 1, 1946)\*

	BABIES		FETAL MORTALITY, PER CENT
	LIVING	DEAD	
First delivery	0	32†	100.0
Subsequent deliveries	35	1	2.8

\*Data on one patient was included in both series.

†One patient had two stillbirths before admission.

The initial fetal mortality rate by selection was 100 per cent. There was one fetal death in 36 subsequent deliveries. The mother who bore the dead infant lost her previous baby from a combination of severe toxemia and a delivery of accouchement forcé and forceps operation elsewhere. This patient was admitted to the hospital on the obstetric service with severe recurrent toxemia and a dead fetus in the uterus. If a correction may be allowed for this infant's death, there was no fetal mortality in the cases in the second series for the last ten and one-half years.

### Histories of the Initial Pregnancies Involving Dystocia

Nine of the first series of 33 patients had been delivered as primigravidas at the clinic. Seven of the second series of 32 patients were delivered for the first time at the clinic. The babies of two of these patients were delivered through the pelvis at the clinic after attempts had been made elsewhere to deliver them. Difficulty in obtaining an accurate history in some cases precluded satisfactory analysis of the cause of the dystocia, although in most cases the cause could be determined rather readily. Actual bony dystocia seemed probable in 11 of the 32 cases encountered between 1936 and July 1, 1946. On the records of 21 of these 32 patients, notes clearly described difficult operative deliveries. These procedures were, in the order of their frequency, forceps delivery (often midforceps and high forceps operations), breech extraction, and version and extraction. Malpresentations of the fetus were important as evidenced by the incidence of eight breech presentations and one shoulder presentation. One patient lost two infants, and both deliveries were by breech extraction. Faulty uterine dynamics, as revealed by notes commenting on "uterine inertia" and "poor progress," were definite in seven cases, and probably the incidence of this important physiologic complication in labor is understated. There were several comments about "soft tissue dystocia" in the histories. There is circumstantial evidence that faulty timing of operative interference

was no maternal mortality in this series. When these data are added to those reported ten years ago, it is found that 64 women had lost 71 babies from dystocia before this study was made. Subsequently they were delivered of 86 babies with three fetal deaths, a gross fetal mortality rate of 3.5 per cent. There was one maternal death early in the first series. The maternal mortality rate for subsequent deliveries was therefore slightly more than 1 per cent. Only two of the 64 women including the one that died are without normal living infants. One of these had normal delivery but lost her infant some months later from nonobstetric causes. She is now pregnant and the chance for a living baby is excellent.

The opportunity for *individual* prenatal care, examination, and study of the safest method of delivery is most valuable in the care of these patients. In these cases the conduct of the first delivery subsequent to the stillbirth from dystocia seemed to determine the outcome in later deliveries. Patients who were delivered successfully through the pelvis continued to have this type of delivery and those who had to submit to abdominal delivery again required this management.

#### Reference

1. Hunt, A. B., and Mussey, R. D.: AM. J. OBST. & GYNEC. 34: 310-315, 1937.

which had been promptly diagnosed by her physician elsewhere. These two babies weighed 5,850 and 4,840 Gm., respectively.

It is important to note that 23 of the 36 deliveries in this series were conducted without resort to abdominal delivery, and all were successful in fetal outcome but one. In this case a macerated fetus was due to severe recurrent toxemia and was delivered spontaneously through a normal gynecoid pelvis. Four patients were allowed a test of labor in the presence of some degree of pelvic contraction, and all were successful in the test. Except for three deliveries by outlet forceps, there was only one operative delivery among the 23 deliveries that were effected without resort to cesarean section. This was an instance of midforceps operation. About one-half of the patients in the group encountered from 1926 to 1935, inclusive, gave evidence on examination of bony disproportion requiring cesarean section. In only about one-third of the deliveries in the second group (1936 to 1946) was abdominal delivery required. This reduced number may indicate a better selection of patients with contracted pelvis for cesarean section.

There were no maternal deaths in our series (1936 to 1946), although there had been one maternal fatality from sepsis following cesarean section in the group of cases previously reported in 1936.

TABLE IV. FETAL MORTALITY IN COMBINED SERIES, JAN. 1, 1926, TO JULY 1, 1946

	BABIES		FETAL MORTALITY, PER CENT
	LIVING	DEAD	
From dystocia in first pregnancy	0	64	100.0
From dystocia in second pregnancy	0	6	100.0
Deliveries subsequent to stillbirth from dystocia	83	3*	3.5
Corrected fetal mortality		1†	1.2

\*One infant died of anomaly on eighteenth postpartum day. There was one intrauterine death before admission from maternal toxemia.

†Mother of this infant was delivered of a surviving infant in 1946.

Data of the two series have been combined in Table IV. These are the total data from the twenty-year period concerning the outcome of deliveries following stillbirth from dystocia. The fetal mortality rate decreased from the initial 100 per cent to an uncorrected figure of 3.5 per cent. If a correction for the two deaths not related to delivery is made, the corrected fetal mortality rate is 1.2 per cent, or one death in 86 deliveries. The mother of the infant represented by this stillbirth was delivered of a living infant in 1946.

A total of 64 women is represented in the combined series. One woman was included in both series. Of these 64, two (only 3.1 per cent), do not have one or more normal living infants. One of these women lost her second infant as a result of severe recurrent toxemia which should probably interdict pregnancy in the future. The delivery of the second infant of the other patient was through the vagina and was normal, but the child died some months later. It was a Mongolian idiot and died of intercurrent disease. This woman is now pregnant and the prognosis for successful result is excellent.

### Summary and Conclusions

The deliveries of 32 patients subsequent to stillbirth from dystocia in primary pregnancies are reviewed. These patients were seen at the clinic from Jan. 1, 1936, to July 1, 1946. A gross fetal mortality rate of one fetal death in 36 deliveries, or 2.8 per cent, was obtained. This infant was dead in the uterus because of a severe toxemia of the mother on her admission to the hospital. There

of twenty-four hours. The method used was the Clark-Collip modification of the Kramer-Tisdall method. In this method, the serum calcium is precipitated as calcium oxalate to which normal sulfuric acid is added. The resulting oxalic acid is then titrated with 0.01 N potassium permanganate. The results with this method have an error of not more than 2 per cent. Every effort was made to observe the details of the method as carefully as possible to keep the results within this limit of error. Phosphorus determinations were also made on each sample of serum, but the results will be disregarded for the purposes of this paper, except to state that the calcium-phosphorus ratio was within normal limits for each sample. No effort was made to control the diet of the patients, other than the routine dietary instructions in our clinic, which include a quart of milk daily. The series includes a total of 185 cases, 119 of which might be called "completed cases," since they were followed throughout the entire course of their pregnancy, labor, and puerperium. However, nine of these cases developed toxemia and were eliminated from the study for that reason. The remaining 66 were "lost" for one reason or another after having at least one calcium determination made, but are used in the study since it was felt that their use would not affect the accuracy of the results. We were unable to obtain sufficient samples during the first trimester of pregnancy to produce an accurate curve for this period. In the "completed cases" a clinical record of the patient's labor was correlated with a record of the calcium determinations. Results were tabulated for each case, and the average of the total determinations for each particular period plotted on a graph as shown in Fig. 1. It is evident from inspection of the curve that there is a depression of the serum calcium during pregnancy which is most marked during the seventh and eighth months. The serum calcium apparently begins to decrease as early in pregnancy as the second or third month, which is what might be expected, since bone formation begins in the fetus as early as the seventh week. There is, of course, a question as to whether the serum calcium determination is an accurate index as to the actual amount of calcium in the body. Since we have no accurate, practical way of determining the amount of calcium in the body tissues, we satisfied ourselves with determinations of serum calcium. We also made no effort to differentiate between ionizable and nonionizable calcium in the blood. Despite the fact that the curve shows a definite depression during pregnancy, the difference between the lowest determination at eight months and the highest determination at two months is only 0.6 milligram. We feel that this difference is sufficiently small to make its clinical importance very doubtful. From our results, we also concluded that it would be impossible to correlate the individual case to this average curve, since the determinations for any particular case in the series did not necessarily show this depression.

For the purposes of comparison, the results obtained in this series were plotted on a graph with the results obtained by Mull and Bill in 1934, Plass and Bogert in 1923, and Widdows in 1924 (Fig. 2). Mull and Bill separated their curve according to the season of the year; January to May, and June to December, as shown above. The curve we obtained would appear to be

## BLOOD CALCIUM: A NORMAL CURVE FOR PREGNANCY\*

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NUMEROUS articles in the literature are evidence of the attention which has been given to the subject of calcium in pregnancy. However, relatively few of these articles deal directly with a series of determinations of blood calcium in pregnant women. Blair-Bell and Hick, in 1909, published the results of in vivo experiments performed on rabbit uteri to determine the response of uterine musculature to certain substances. Among other results, the response of the pregnant uterus to the intravenous injection of calcium salts was very marked, with the same type of uterine contraction as seen in labor. From their findings, they concluded that labor was not the result of any one reagent, but expressed the belief that calcium salts circulating in the blood, or excreted by the uterus, played the most important role in that connection; acting in conjunction, possibly, with certain other substances, such as pituitrin, secreted by the endocrine glands. Danforth and Ivy in 1939 published the results of a similar series of experiments in vivo performed on the uteri of dogs and rabbits in an effort to disprove or confirm these findings of Blair-Bell. An interesting part of their work was the use of sodium hexameta-phosphate intravenously to combine with calcium and prevent manifestation of its physiologic action. Their results clearly demonstrated that calcium played a vital role in the motor activity of the uterine muscle, even pituitrin and ergotrate having no effect in the absence of calcium. They suggested the possibility that physiologic variations in the reactivity of uterine muscle during labor might result from physiologic changes in the availability of calcium ions.

This article does little to confirm or disprove these interesting findings. It is simply a report of a series of cases studied at the University of Kansas Hospitals in an effort to establish a "normal" level of serum calcium for pregnant women. It was thought at the onset of the study that if calcium did play a vital role in the onset of labor, such information might be obtained if the serum calcium was correlated with the patient's progress throughout her pregnancy, labor, and the puerperium. Only primiparas were used in the series, and all determinations were made by the author after a practice period in which to become familiar with the method and eliminate, as far as possible, all sources of error. An attempt was made to follow each case throughout the course of her pregnancy, labor, and puerperium, with blood being drawn at monthly intervals during the pregnancy, once during labor, and once in the immediate puerperium, not more than fourteen days post partum. The samples, after being obtained, were kept at a cool temperature and, after the blood coagulated, the serum calcium was determined within a maximum period

\*Presented before the Central Association of Obstetricians and Gynecologists, Fourteenth Annual Meeting, Chicago, Ill., Sept. 19 to 21, 1946.

roughly an average between these two. Why the determinations obtained by Plass and Bogert should be so much lower than those in this series and that of Mull and Bill could be explained, perhaps, on the basis of the small number of determinations, since the same method of determination was used in all three series. It is interesting that, despite this fact, the general contour of all three curves is roughly similar, although the results of Mull and Bill and the present series most nearly correspond. Neither Mull and Bill nor Plass and Bogert ran determinations during labor, but from their results concluded that the serum calcium rose sharply after delivery. The results of the present series differ from those conclusions, since they indicate that this elevation occurs to a certain extent at the time of labor, but that this elevation is simply a continuation of the rise which began at the ninth month. The series of Widdows was somewhat incomplete, but very roughly corresponds to the findings in the other series, as shown in Fig. 2.

From the 110 "completed cases" in the present series, 20 cases having "short" labors, averaging seven hours and five minutes in length, were selected and the average of the serum calcium determinations for these 20 cases was determined with the following results:

MONTH	SERUM CALCIUM	DETERMINATIONS
Second	10.40	2
Third	10.03	3
Fourth	9.93	7
Fifth	9.72	11
Sixth	9.83	14
Seventh	9.66	15
Eighth	9.64	15
Ninth	9.78	19
Labor	9.96	20
Post partum	10.22	18

Similarly, 20 cases of "long" labor, averaging twenty-eight hours and thirty-five minutes in length, were selected and the following results obtained:

MONTH	SERUM CALCIUM	DETERMINATIONS
Second	9.91	1
Third	9.57	2
Fourth	9.95	9
Fifth	9.89	10
Sixth	9.78	14
Seventh	9.69	14
Eighth	9.83	18
Ninth	9.88	20
Labor	10.01	19
Post partum	10.35	20

These results are shown in Fig. 3. It was not felt that the differences in serum calcium determinations between the cases of "long" labor and "short" labor were sufficiently marked to be of any significance. As a matter of fact, from observation, it is evident that the two curves correspond rather closely.

Forty-six "plus" cases in which the serum calcium determinations ran consistently above the average curve had an average blood loss of 213 c.c. with an average labor of fifteen hours and fifty-seven minutes. Twenty-two "minus" cases with the serum calcium determinations consistently below the average



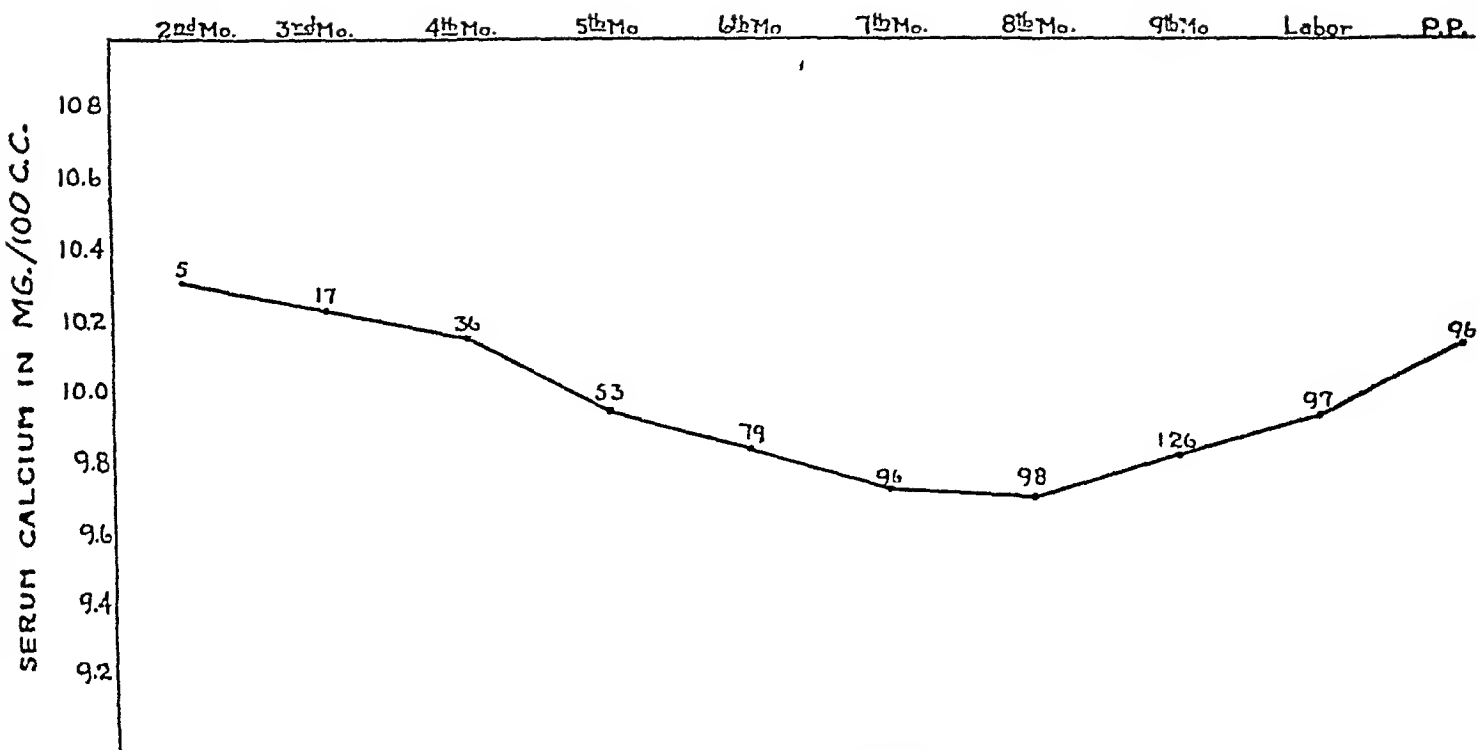


Fig. 1.—Serum calcium in pregnancy.

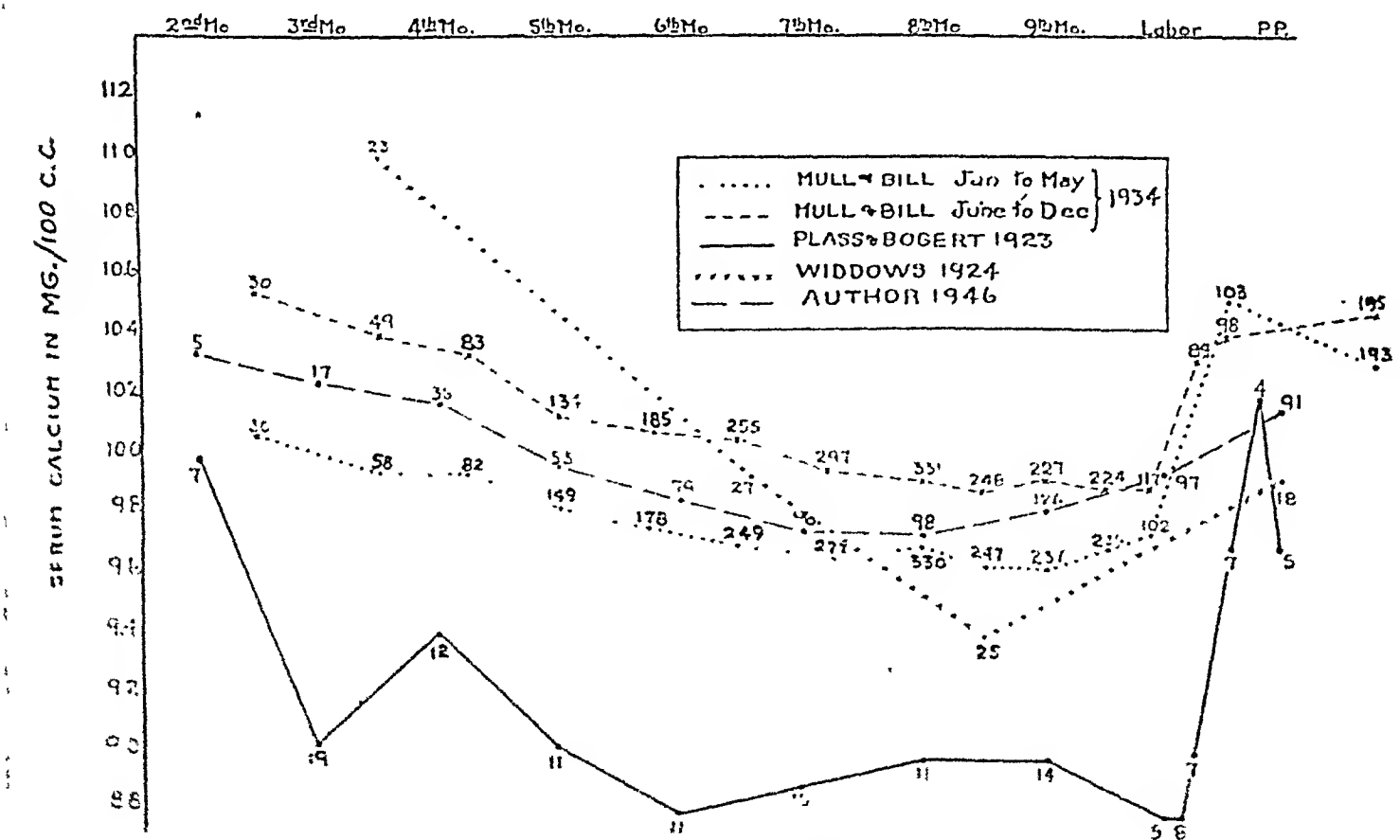


Fig. 2.—Serum calcium in pregnancy.

curve had an average blood loss of 157 c.c. with an average labor of eighteen hours and twenty-seven minutes. These differences are not considered to be sufficiently great to be of any statistical value.

It has been previously mentioned that nine of the cases in the series developed toxemia. It is interesting that the curve of serum calcium determinations in these cases is very bizarre, not conforming at all to the average curve which has been presented. For the purposes of interest only, these results are shown in Fig. 4. It was felt that the number of determinations was too small to be of value in reaching any conclusions.

In conclusion, we have tried to demonstrate a "normal" curve of serum calcium in pregnancy, labor, and the immediate puerperium. The results indicate a depression of the serum calcium during pregnancy which begins to rise at the ninth month, the elevation continuing through the period of labor and almost reaching its early pregnancy level by the end of the immediate puerperium. This depression of the serum calcium is sufficiently small to make its clinical significance questionable. Results of the study would tend to indicate little relationship between the serum calcium level and the length of labor or amount of blood loss.

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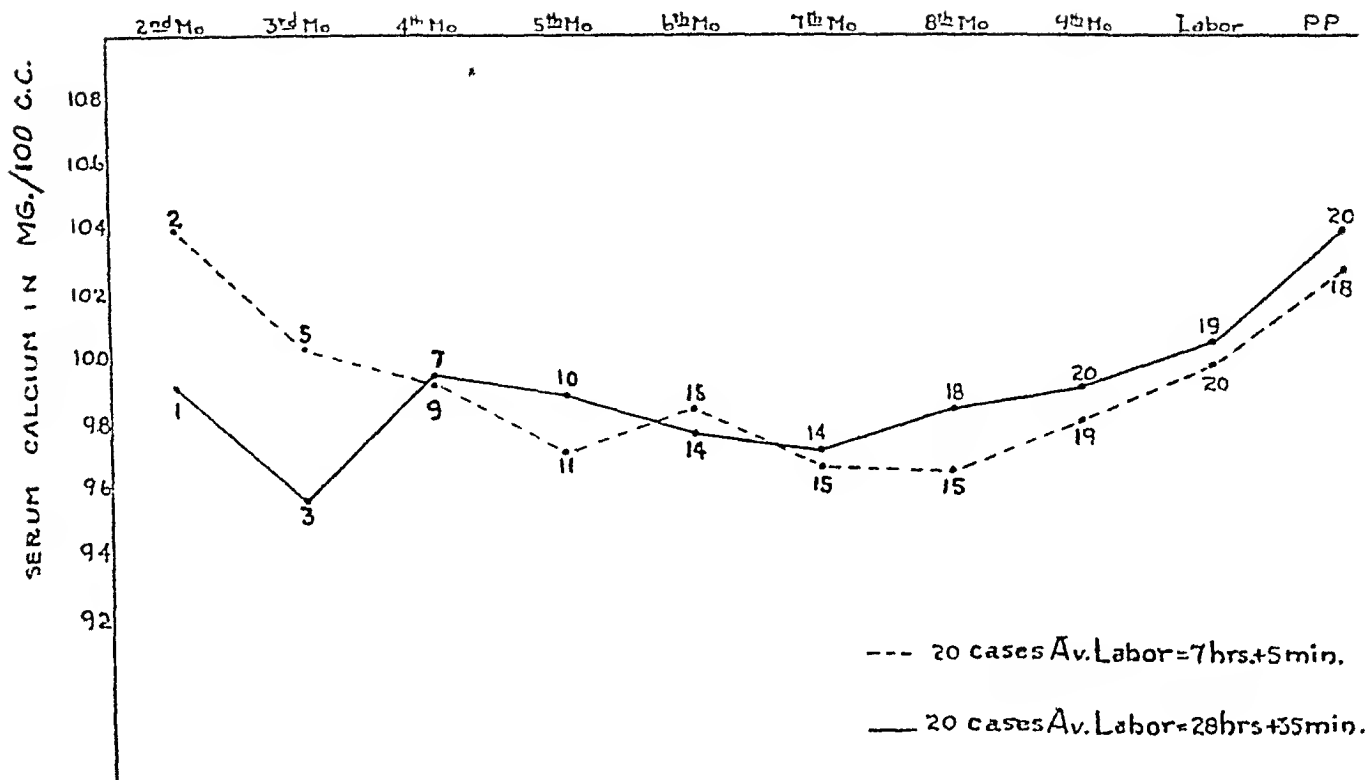


Fig. 3.—Serum calcium in pregnancy.

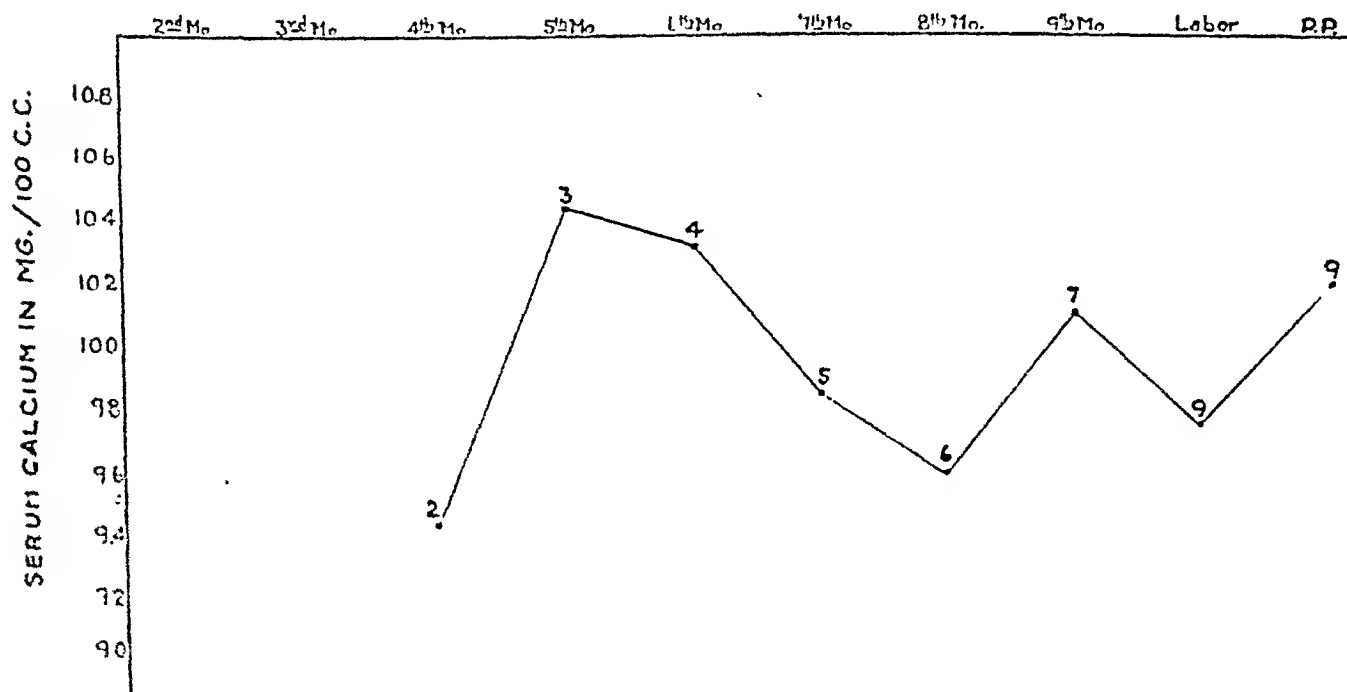


Fig. 4.—Serum calcium in toxemia.

TABLE I

GROUP*	SUM IS AND PS (CENTIMETERS)	PATIENTS NUMBER	DELIVERY				FETAL DEATH	
			SPON- TANEOUS	NECESSARY OPERATION		NUMBER	PER CENT	
				NUMBER	PER CENT			
1	12.0	2	1	1	50.0	0	-	10.3
2	12.0-12.4	3	1	2	66.6	1	33.3	
3	12.5-12.9	5	1	4	80.0	0	-	
4	13.0-13.4	7	2	3	42.8	0	-	
5	13.5-13.9	12	6	4	33.3	2	16.6	5.5
6	14.0-14.4	22	10	5	22.7	2	9.1	
7	14.5-14.9	25	14	6	24.0	1	4.0	
8	15.0-15.4	16	5	6	37.5	1	6.3	
9	15.5	48	32	6	12.5	2	4.1	

\*Note that a definite "break" in the fetal death rate seems to occur between Groups 5 and 6. Also note that two patients in Group 1 gave birth to living children.

The fetal death in the second group of patients resulted from a craniotomy necessitated by insurmountable midplane disproportion after the head passed through the pelvic inlet. The other two infants were born spontaneously and by low forceps, respectively.

In the third group, the largest infant was born by cesarean section, the next largest by midforceps, two smaller by low forceps operation, and the smallest spontaneously.

### Prediction of the Course of Labor

In addition to analysis of the actual outcome of labor, the present report embodies a survey of the results of "prediction" of its course. In many instances, prediction was made after termination of labor, but may be accepted as reliable for the purposes of this report, since it was done without knowledge of the outcome.

Pelvic measurements of the patients in this series were graphically portrayed by means of the method recently described by Mengert and Eller.<sup>5</sup> Fig. 1 illustrates the midplane of one of these patients (dotted lines) in immediate comparison with the normal prototype (solid lines). A plastic transparent model, Fig. 2, representing a small, medium, or large fetal head, was superimposed on the pelvic diagram. The relationship between the pelvic diagram and the plastic cutout permits understanding of the possibility of passage and of direction. In event of forceps delivery, superimposition of the fetal head model in various positions often indicated the mechanisms and rotations to be employed.

It was recently demonstrated<sup>3</sup> that there is no constant relation between fetal weight and head diameter. However, the length or weight of the fetus is relatively of little concern from the standpoint of labor, in comparison to the size of the head. It is of considerable prognostic significance to be able to classify fetal heads roughly as small, medium or large. Abdominal palpation can supply this information. Also, the head can be measured from the films used for pelvic mensuration, provided the child is near term and the head is fixed.

Fig. 3 depicts the midplane, shown in Fig. 1, with the head model superimposed. Obstruction to the passage of a large fetal head can be readily visualized. It is equally apparent that a small head, represented on the model by the innermost diameter, will be able to traverse the midplane. Unfortunately for this patient, the fetal head was large, and difficult forceps rotation and extraction of a child lying in persistent occiput posterior, performed after two hours of complete cervical dilatation with the vertex well below the spines, re-

# EXPERIENCE WITH MIDPELVIC DYSTOCIA\*

## Preliminary Report

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CONTRACTION of the pelvic midplane sufficient to necessitate craniotomy can occur<sup>1</sup> in a patient with inlet and outlet measurements at the lower limit of normal. On the other hand, midpelvic dystocia is unlikely in patients with average or larger inlet and outlet measurements. It has been suggested<sup>2, 3</sup> that midpelvic capacity is best evaluated by summation of the interspinous and posterior sagittal diameters. Guerriero, Arnell, and Irwin<sup>2</sup> believe that dystocia may be expected when the sum is 13.5 cm. or less, while Weinberg and Seadron<sup>3</sup> favor 13.0 centimeters. There is need for collection and evaluation of accurate statistics on the pelvic midplane.

## Patients

Serious interest in this subject at Parkland Hospital began a year ago and by June 1, 1946, the pelves of 140 patients were evaluated by a combination of radiographic mensuration<sup>4</sup> and graphic portrayal.<sup>5</sup> Because of film shortage, the first 102 patients included only those with varying degrees of contraction of one of the three essential pelvic planes. Later, some 12 women with unexplained stillbirth, or previously difficult forceps operations, were recalled and their pelves measured. Finally, in March, 1946, each primigravida and all multigravidas with previous difficulty were routinely submitted to radiographic mensuration and graphic pelvic portrayal. Preparation of this report began six weeks later and, therefore, only 26 of these women are included, although routine mensuration continues.

A résumé of the outcome of delivery in relation to the sum of the transverse and posterior sagittal midplane dimensions appears in Table I. In general, it will be noted that the frequency of necessary delivery operation and the rate of infant death decrease as this sum increases. It is, however, of considerable interest to note that in several instances vaginal delivery was accomplished successfully in spite of seemingly severe contraction. Pelvic contraction does not necessarily imply arrest of labor, and impressions gained solely from pelvic mensuration without consideration of size of the baby are often subject to error.

Of ten patients with midplane measurements totaling less than 13 centimeters (Groups 1, 2, and 3 of Table I), eight were delivered vaginally, three of them spontaneously.

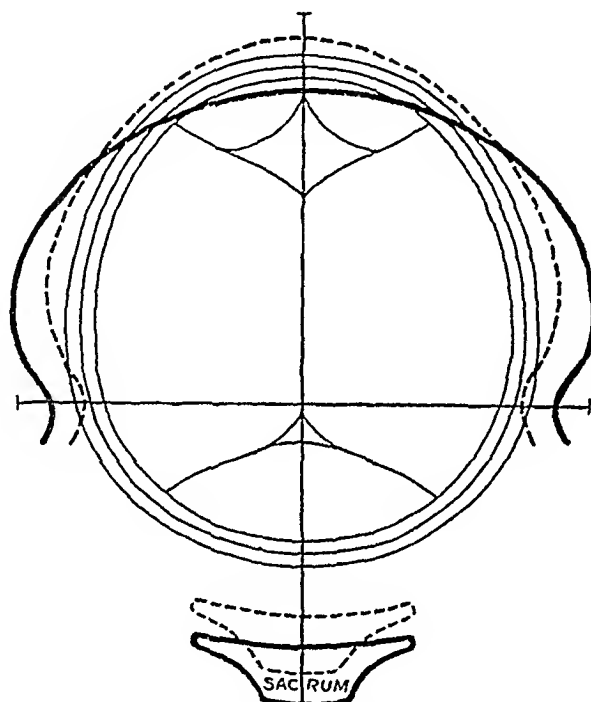
In two patients (Group 1) the sum of the interspinous and posterior sagittal diameters was less than 12 centimeters. One was delivered spontaneously of a 2,912 Gm. infant. The other, with an unusually ample forepelvis, required midforceps operation, but produced a living 4,571 Gm. child!

\*Presented before the Central Association of Obstetricians and Gynecologists, Fourteenth Annual Meeting, Chicago, Ill., Sept. 19 to 21, 1946.

sulted in a stillbirth. Autopsy revealed intracranial hemorrhage and dislocation of the second cervical vertebra.

"Prediction" was made in each of the 140 women in terms of "easy" or "difficult" vaginal delivery, or of necessity for cesarean section. "Easy vaginal delivery" was defined as spontaneous labor or elective low forceps operation, except when fetal death or injury from birth trauma resulted. "Difficult" was defined as vaginal operation necessitated by more than two hours of second stage with the cervix dilated and effaced.

A prediction of difficult delivery was made in twenty-five patients. Actually cesarean section was performed on five of them, thus eliminating them from proof of predictability. In seventeen of the remaining twenty patients, difficulty was experienced (Table II).



	Normal	Patient
Anteroposterior	11.5	11.9
Transverse	10.5	9.2
Posterior Sagittal	5.0	4.5

Fig. 3.—There is no room for the large size head in occiput posterior, in this midplane. The result is similar no matter whether the head is fitted in the fore or in the hind pelvis. On the other hand, the smallest size will go through.

Easy vaginal delivery was predicted for 115 patients, but 22 experienced some difficulty, as noted in Table III. In the group of 22 patients with incorrect prediction, there were three breech deliveries, two elective and unindicated forceps operations, and six patients with prolonged labor (more than thirty hours), thought to be due to uterine inertia rather than to bony dystocia.

### Discussion

There is more to bony dystocia than pelvic mensuration. Fetal size, and moldability of the head, fetal attitude, and the force of uterine contraction must also be considered. Of these, fetal size alone is susceptible to quantitative

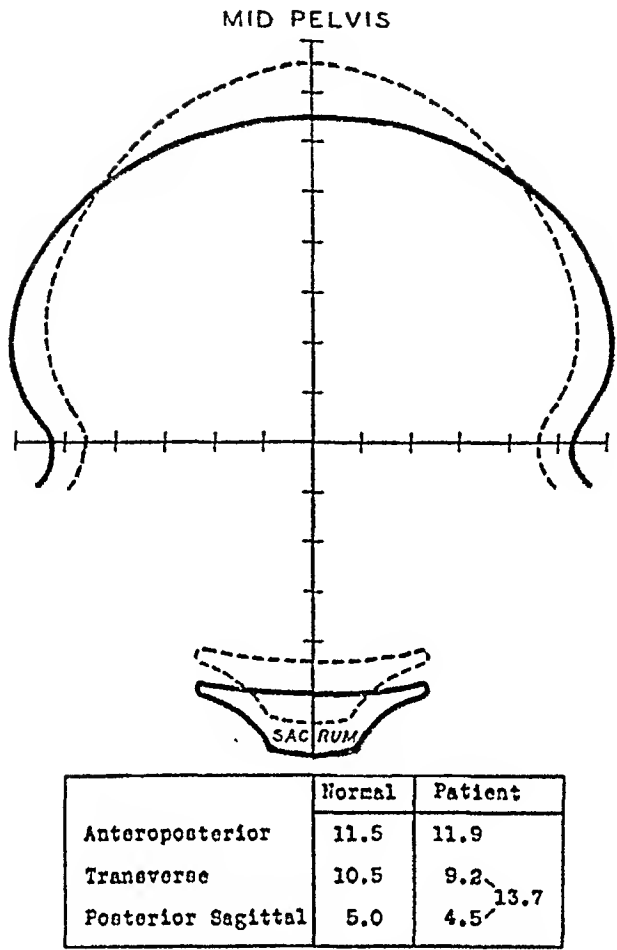


Fig. 1.—Diagram of a moderately contracted midplane.

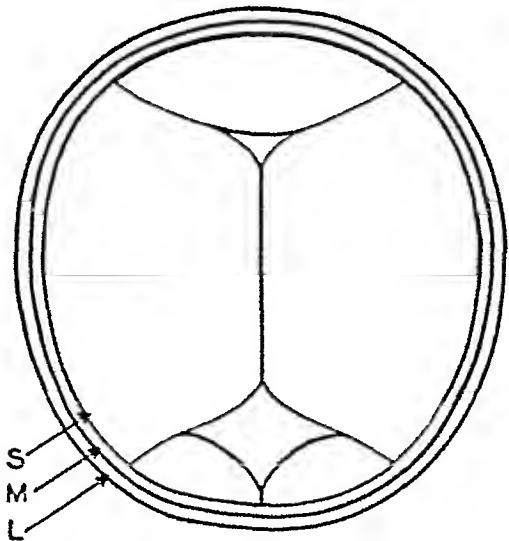


Fig. 2.—Transparent, plastic head model, with three head sizes: small, medium, and large.

cent). On the other hand, term-sized children were born alive through the two smallest midplanes (12.0 centimeters) in the series.

When midpelvic capacity is reduced to dangerous limits, prediction of the outcome of labor, and foreknowledge of the mechanisms to be employed with forceps operation are greatly augmented by employment of transparent cephalic models superimposed upon a midplane diagram.

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TABLE II. DYSTOCIA PREDICTED

17 Patients	
<i>Position:</i>	
Occipitoanterior	6
Persistent occipitoposterior	8
Persistent occipitotransverse	3
<i>Results:</i>	
Spontaneous delivery	1
(3¼ hours second stage, neonatal death from intracranial hemorrhage)	
Low forceps indicated	4
Midforceps	10
(1 stillborn, intracranial hemorrhage)	
Craniotomy	2
(Midpelvic arrest)	
Fetal loss	4 (23.5%)

TABLE III. DYSTOCIA NOT PREDICTED

22 Patients	
<i>Position:</i>	
Occipitoanterior	6
Persistent occipitoposterior	6
Persistent occipitotransverse	7
Breech	3
<i>Result:</i>	
Low forceps	5
Midforceps	14
Breech extraction	3
Fetal loss	5 (22.7%)

determination. Commonly, obstetricians are concerned with weight of the baby. On the other hand, the size of the head is more important from the standpoint of prognosis of the outcome of labor than the weight or length of the infant. Although fine gradations may not be feasible, radiographic fetal cephalometry permits classification as large, medium, or small.

In the great majority of patients, current methods of mensuration will reveal an obviously ample pelvis, with no reason to anticipate bony dystocia at any level. In the relatively small group with borderline inlet capacity, careful clinical observation of the degree of disproportion and descent, and of the forces and progress of labor, will generally allow an early determination of the procedure of choice. With outlet contraction, observation of progress is clinically unsound, and arbitrary decision must be made in advance.

Midplane contraction is somewhat analogous to outlet contraction, because observation of the progress of labor, with intent to interfere abdominally in case of arrest, is seldom feasible. Serious dystocia at the midplane is encountered more frequently than at the outlet, but midpelvic capacity is seldom evaluated prenatally. Therefore, universal effort directed at collection and evaluation of midplane dimensions and their effect on the course of labor is urgently needed.

Evaluation of midpelvic capacity of a small selected series of 140 patients showed that dystocia and fetal calamity were more common when the sum of the interspinous and posterior sagittal diameters was less than 14 centimeters. Thus, there were three fetal deaths in 29 such patients (10.3 per cent) as opposed to six among 111 patients with a sum of 14.0 or more centimeters (5.5 per

6 per cent, 3 per cent, and 0.2 per cent. These figures demonstrated that only with three smears and three cultures could the diagnosis of gonorrhea be ruled out with any reasonable assurance.

The question of cure is even more difficult. Most recent literature on gonorrhea deals with the relative merits of one or another technique of administration of sulfonamides or penicillin. But a survey indicates a wide disparity in the criteria used for cure, varying from two negative cultures in six days to ten negative cultures in three months. In this particular series, only 431 of the women were treated by the clinic or the quarantine hospital, the rest either being sent to private physicians or other clinics, or else leaving town. Cures were effected by one or two courses of sulfathiazole or penicillin or one of each, in 401 women, that is, 93 per cent. The remainder required more treatment. There were four failures after four courses of penicillin. As it is not the purpose of this paper to compare techniques of cure, the discussion is limited to what constitutes a cure and how it affects the handling of the individual woman. More than one-fourth of the cases were in quarantine and incapable of being reinfected. While the possibility of reinfection of the others existed, it was minimal due to the careful contact histories obtained, and, where any doubt existed, the case was considered a reinfection. The difference between the two groups of figures was found to be insignificant, a phenomenon reported by many other authors, so that the 431 cases were considered in one series.

A single culture twenty-four hours after the completion of ten days' treatment with 2.0 Gm. of sulfathiazole or after the administration of 200,000 Oxford units of penicillin in four two-hourly doses of 50,000, missed 84 per cent of the failures to cure. A smear and a culture missed 65 per cent. A second culture forty-eight hours after treatment missed 72 per cent of the failures; the second smear and culture missed 37 per cent. Within ten days after treatment, a total of three cultures missed 24 per cent, and a combination of three smears and cultures missed 8 per cent of the failures to cure. Thus, by setting up any combination of smears and cultures as a criterion, the rate of cure will read almost any percentage.

That these figures are not usually high is borne out by the findings of Koch<sup>1</sup> and his co-workers in San Francisco. Dealing chiefly with males, they reported 71 per cent of failures missed by the first posttreatment culture and 62 per cent on the second. Blair,<sup>2</sup> at the Women's Federal Reformatory in West Virginia, confirms the observation with the remark: "In most cases (of cure failures) positive tests were obtained by the third check, although several were not found until the fifth or sixth specimens."

The importance of time among the criteria of cure cannot be overemphasized. Considering only the women in quarantine, incapable of being reinfected, the failures of treatment with sulfathiazole were first picked up as follows: three within the first two weeks after completion of treatment, seven in two to four weeks, and two cases after one month. With penicillin, while most of the failures were detected in the first fortnight, two cases merit brief description: Bernice M., treated with 200,000 units of penicillin on January 20, had three successive negative smears and cultures in the following two weeks. She was "cured" by the standards used there and at a great many other institutions. But just before release from jail on March 27, she had a positive smear culture. Catherine B. was treated on February 11 with penicillin and considered cured after three successive negative smears and cultures. But on May 20, just prior to release from confinement she had a positive culture. Thus the organisms, apparently destroyed by penicillin in these two women, became manifest two and three months respectively after pronouncement of cure and noninfectiousness by prevailing standards. Attention is invited to Koch's report

## AN EVALUATION OF THE CRITERIA OF DIAGNOSIS AND CURE OF GONORRHEA IN THE FEMALE\*

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THE responsibility of making a diagnosis of gonorrhea or of ruling it out in an adult female is a serious one for any doctor because of the social, legal, and public health aspects. The gynecologist and the obstetrician are particularly concerned and should take the lead in establishing, at least for themselves, adequate criteria on which to make their decision. At present, in most communities, the diagnosis is a matter of clinical judgment supported by some type of laboratory evidence; the Public Health Service and the Armed Forces go further in their laboratory requirements, but few gynecologists are aware of the limitations of laboratory reports to support the statement that any individual woman either has or does not have gonorrhea, or that she is or is not cured of it.

### Material

The material of this survey consists of 598 women from the Cincinnati Health Department clinic and from the Quarantine Hospital of the Municipal Workhouse, on whom over 6,100 smears and 3,200 cultures were reported. A good contact history was obtained on almost all of these cases by highly trained nursing personnel, and clinical observations on all of them were adequately made by one or more physicians with specialized training in venereology or gynecology.

The smears and cultures were done by the City of Cincinnati Health Department in its distinctly better than average laboratory. While specialized centers have reported culture accuracy greater than was found in this series, the value of this survey lies in the picture it gives of gonorrhea in the average large community with ordinary diagnostic facilities. It is the situation that faces most practicing physicians and the vast majority of clinics dealing with this problem. The number of cases is large enough to have statistical significance, and the purpose of the review is to stimulate the acceptance of criteria of diagnosis and cure that are actually adequate.

In trying to make a diagnosis of gonorrhea in the presence of clinical findings or a contact history or both, considerable reliance was formerly placed on a single smear. This also held true for ruling out gonorrhea in pregnancy, before marriage, for foodhandler examinations, employment examinations, institutional admissions, and for contacts. In this series of 598 women determined as being infected with gonorrhea, a single smear missed 59 per cent of the cases. On the other hand, a single culture missed only 38 per cent of them. The combination of a smear and a culture missed only 28 per cent, that is, only half as many as a single smear. When the suspects not already diagnosed were given two examinations at least twenty-four hours apart, the percentage of missed cases fell, on two smears, to 24 per cent, on two cultures, to 10 per cent, and on two of each, to 6 per cent. On three examinations the figures were, respectively:

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40 per cent better results, and the Mueller-Hinton starch agar 27 per cent better results than did the Difeo preparation. The actual technique followed was that of Carpenter<sup>5</sup> with minor modifications. In the earlier days of the study, before numerous processing errors were noted and corrected, there were many false negatives not ascribable to the correctly performed culture method, but all cases are included in this series so that the advantage of cultures over smears does not reach the two to three figure reported in the literature.

In making a diagnosis of gonorrhea, the culture technique in this study, uncorrected, proved 1.7 times more accurate than the smear. In detecting failures of cure, however, the culture was not significantly more accurate. This suggests the importance of the biologic factor referred to above. Confirmation is found in comparing the results of smears and cultures taken at the same examination. Of these, false negative reports were given 742 times, of which both smear and culture were wrongly negative on 183 occasions, only the smear wrong 240 times, and only the culture wrong 136 times. In breaking down the ratio of false negative reports it was found that in diagnosis the culture was 1.5 times more accurate than the smear (292:193) whereas in the detection of treatment failures there was no significant difference (133:126).

Incalculable social harm can be done by the making of an erroneous diagnosis of gonorrhea, so that the question of false positive reports deserves attention. In this series of 9,300 tests there were only 56 false positive smears and eight false positive cultures. Of these, eight smears and one culture were from eight women who did not have gonorrhea; they represent pure laboratory errors. The remainder were in women who were treated, some with sulfonamides and some with penicillin, and there is a question of whether they represent laboratory errors or biologic peculiarities. All of these women had a long succession of negative smears and cultures following the false positive findings. The time elements were: in the first three days after penicillin treatment, 26 positive smears with negative cultures, and two positive cultures with negative smears; in from four to fourteen days, eight and three respectively; in the third week after treatment, 11 positive smears with negative cultures, and one in which both smear and culture were positive. In many clinics this case would have represented a treatment failure, but in the absence of clinical findings or contact history, and in the presence of seven subsequent negative smears and cultures without intervening treatment, the case was indubitably a laboratory error. False positive errors are due usually to the presence of other *Neisseria* such as: *catarrhalis*, *sicca*, *flava*, and *intracellularis*. These are indistinguishable by ordinary staining technique but may be differentiated from *Neisseria gonorrhoeae* by subculturing in certain sugars.

In this connection there may be mentioned briefly the results of a study, as yet incomplete, of 97 cases diagnosed as vulvovaginitis in children. A careful review of the records with particular reference to clinical findings and smears and cultures without treatment, or after extensive treatment, suggests that 45 of these were not gonorrheal, 23 were doubtful, and only 29 actually were due to the gonococcus. Of 821 smears, only 67 per cent gave correct results, but of 477 cultures, 97 per cent were correct. Of the false positive results, 89 per cent

of 38 per cent of his failures in men after five or more weeks of negative observation. Thus, the glowing reports of cure in the literature must be slightly discounted unless the cures were confirmed over a period of months. The importance of this to the individual woman and her husband is obvious.

### Discussion

In analyzing why smears or cultures in such a high percentage of cases fail to reveal the presence of the gonococcus, three factors come to mind. The first, in connection with putative cures, is the biologic one, and it is largely in the realm of theory. Questions may be asked, such as: Can sulfonamides or penicillin destroy only a certain percentage of organisms, or inhibit them, the remaining few lurking in the body to reproduce slowly and become detectable only after the passage of time? If so, then much work is needed to throw light on what the time factor is. Does the gonococcus exist in small numbers in secretions of the genital tract out of biologic contact with the blood stream and hence exempt from the action of sulfonamides or penicillin? If so, consideration must be given to adjuvant local treatment. In any case more knowledge is needed.

The second factor is the method used for taking the specimens. It was found that the percentage of false negatives dropped noticeably when the cervix was first wiped out thoroughly, and any tenacious mucus removed by winding on a thin swab. The swab for taking the specimen was inserted deep into the canal up to the internal os and pressed vigorously against the walls of the canal, while at the same time the jaws of the bivalve speculum were partially closed against the cervix so as to milk out cervical secretions. Better results were also noted just before, during, and immediately after menstruation.

The third factor is the laboratory procedure. Dealing for the moment only with false negative reports, the commonest laboratory error in examining smears is a failure to search long and thoroughly enough for the occasional Gram-negative intracellular diplococcus. It is a time-consuming process that few laboratories can afford, and for that reason a great many laboratory directors prefer to receive cultures for diagnosis.

The superiority of cultures over smears has been repeatedly proved but the wider use of cultures has been hampered by the technical difficulties of processing. The gonococcus is delicate, and numerous bacteriologic requirements must be met before reliance can be placed on negative reports. Actually, however, the difficulties are not formidable, and once a routine is established the use of cultures becomes quite easy for the doctor, the clinic personnel, and the laboratory. For private practice a messenger service to a laboratory within a few hours of procuring the specimen seems essential, but attention is invited to the preliminary work in North Carolina reported by Hirschberg,<sup>2</sup> using a solid medium with which cultures may be sent by mail.

In this study the medium used was a chocolate agar (Difco bacto-proteose No. 3 and bacto-hemoglobin), which is in common use. That even greater accuracy may be obtained with other media is demonstrated by a recent work of Weller and Williams<sup>4</sup> showing that a modified Peizer plasma-hemoglobin gave

## PENICILLIN AND ACUTE PUERPERAL MASTITIS\*

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**A**CU TE mastitis is an aggravating complication of the puerperium. The rapid and specific action of penicillin, when used early in this infection, is dramatic. Neither local nor systemic sulfonamide therapy is satisfactory. The initial favorable results with penicillin have stimulated further investigation of this method of therapy and can be reported now.

*Incidence of Puerperal Breast Infections.*—It has long been recognized that acute puerperal mastitis is an institutional disease, but Fulton<sup>1, 2</sup> recently re-emphasized this point. Apparently there is a geographical variation in the number of cases encountered. In this country the accepted figure is from 0.5 per cent to 2.0 per cent, and the incidence of this series of cases falls within that average. In England, Fulton found a breast abscess which either required incision and drainage or evacuated itself spontaneously in 16 per cent of patients delivered in the hospital, while 3.5 per cent of those delivered at home developed suppuration of the breast. In a later study of 250 patients, 25 per cent developed an abscess. Such an incidence is difficult to explain, especially when strenuous efforts were made during the study of the second series to reduce the frequency of the disease.

*Penicillin and Breast Infection.*—Early experimental investigation with penicillin demonstrated its value in soft tissue infections. This experience suggested its clinical trial in inflammatory diseases of the breast. Fraser<sup>3</sup> treated 15 patients by aspiration and instillation of penicillin into the abscess cavity, resulting in resolution without drainage in only three cases. Hodgkinson and Nelson<sup>4</sup> in 1945, and Power and Cravotta<sup>5</sup> in 1946, reported excellent results using intramuscular penicillin during the cellulitis phase of the disease. Further clinical trial has justified these original claims.

*Present Series of 73 Cases.*—This report is based upon the experience of treating 73 infected breasts observed since 1942. The definition of puerperal breast infection used for this group was based upon well-established clinical facts. The history as obtained from each patient was essentially identical: sudden onset of pain in the breast, followed shortly by chills and hyperpyrexia. The average temperature upon admission was 101.6° F. although variations as high as 106° F. were encountered. The leucocyte count was as high as 31,000, averaging 15,600, with corresponding elevations in neutrophile percentage. Examination usually disclosed a mass in the breast underlying an area of erythema. Occasionally the involvement was diffuse. Simple congestive states were eliminated by the time of onset which averaged twenty-four days from the time of delivery. Only one patient experienced trouble as early as the twelfth postpartum day.

While the majority of infections developed in the postpartum period, seven of them cannot be considered true instances of puerperal mastitis. In the latter classification are two patients whose breast suppuration was neither related to pregnancy nor lactation. Prepartum breast infection developing in the eighth

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were smears. It is probably safe to say that smears are not to be relied on for either a diagnosis or a criterion of cure, and that even cultures of these children require subculturing in the carbohydrates before designating the gonococcus as the offending organism.

### Summary

1. This study involves over 6,100 smears and 3,200 cultures in the diagnosis of 598 cases of gonorrhea in the adult female, and the treatment of 431 of them.

2. A single smear missed 59 per cent and a single culture, 38 per cent of the infected cases, but three smears and three cultures missed only 0.2 per cent. As a criterion for cure, three smears and three cultures in the ten days after treatment missed 8 per cent of the treatment failures.

3. The culture proved 1.7 times as accurate as the smear for diagnosis but no more accurate than the smear for the detection of treatment failures.

4. False negative laboratory reports are due to (a) some biologic factor of which little is known, (b) the technique in taking specimens, and (c) laboratory errors. These, in the case of smears, are most commonly the result of insufficient study of the slide, and in the case of cultures are due to the delicacy of the organism and its need for special handling.

5. False positive results may be socially disastrous. They are found rarely with a properly performed culture.

6. In vulvovaginitis, of which 97 putative cases were studied, the smear proved of little value because of the high percentage of false positive reports. Cultures, including sugar differentiation, should be the sole method of diagnosis.

7. In adult females both smears and cultures should be used, as the accuracy of diagnosis is increased significantly. The smear offers an opportunity for a rapid report if it is positive. The culture technique presents some difficulty for other than institutional practice, but it is feasible under most circumstances.

8. Stricter and more uniform criteria for the diagnosis and determination of cure of gonorrhea in the adult female should be established by professional agreement. The minimum proposed to rule out gonorrhea is three smears and cultures, and to determine a cure, a succession of smears and cultures over a period of two months.

Appreciation is expressed to Dr. Carl A. Wilzbach, Health Commissioner of the City of Cincinnati, for permission to use the material surveyed and for many helpful suggestions; to Dr. A. H. Rodenburg, of the Cincinnati Health Department staff for advice with clinical problems, and to Mr. Otto P. Behrer, City of Cincinnati Bacteriologist, for help with laboratory problems.

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TABLE I. MILK SPECIMEN OBTAINED BEFORE ADMINISTRATION OF PENICILLIN

NUMBER	MILK CULTURE	BACTERIAL COUNT PER C.C.
1	<i>Staphylococcus</i>	
2	<i>Staph. aureus</i> , hemolytic	3,000
3	<i>Staph. albus</i> and <i>Staph. aureus</i>	1,840
4	<i>Staph. aureus</i>	20,600
5	<i>Staph. aureus</i>	4,600
6	<i>Staph. aureus</i> and <i>Staph. albus</i> (coag. pos.)	980
7	<i>Staph. aureus</i> (coag. pos.), nonhemo- lytic streptococcus	1,200
8	<i>Staph. aureus</i>	7,500
9	<i>Staph. aureus</i> (coag. pos.)	7,500
10	<i>Staph. aureus</i> (coag. pos.)	9,200

TABLE II. 300,000 OXFORD UNITS PENICILLIN IN OIL AND WAX GIVEN INTRAMUSCULARLY. SPECIMENS OBTAINED EIGHT AND ONE-HALF HOURS AFTER ADMINISTRATION

PENICILLIN BLOOD LEVEL	MILK CULTURE	BACTERIAL COUNT PER C.C.	PENICILLIN MILK LEVEL
.062	<i>Staphylococcus</i> and a few colonies of streptococcus		0
.030	<i>Staph. aureus</i> , hemolytic	2,000	0
.061	<i>Staph. aureus</i>	1,800	0
.062	<i>Staph. aureus</i>	9,400	0
.310	<i>Staph. aureus</i>	1,800	0
.248	<i>Staph. aureus</i> and <i>Staph. albus</i> (coag. pos.)	5,060	0
	Streptococcus, hemolytic		
.200	<i>Staph. aureus</i> (coag. pos.)	4,800	0
	Nonhemolytic streptococcus		
.128	<i>Staph. aureus</i>	4,000	0
.240	<i>Staph. aureus</i> (coag. pos.)		0
.240	<i>Staph. aureus</i> (coag. pos.)	20,000	0

breast. The opinion that lactation should be inhibited is strengthened by the knowledge that the concentration of penicillin attained in breast milk is insufficient to sterilize the milk. There has been no reactivation of infection since adopting this plan.

*Breast Prophylaxis.*—Proper breast hygiene is stressed as a measure of prophylaxis. Stander<sup>9</sup> places the responsibility of the infection directly upon the attending physician or nurse, laying the cause to neglect.

Numerous bacteriologic studies have demonstrated that the usual puerperal breast abscess is caused by a coagulase-positive strain of staphylococcus. Routine culture from the throats of the newborn, the mother, and their attendants are commonly positive for *Staphylococcus aureus*. DeLee<sup>10</sup> stressed for many years the frequency with which staphylococci could be cultured from breast milk. In a relatively recent study, Schlaeppli<sup>11</sup> found *Staphylococcus albus* and *Staphylococcus aureus* constant contaminants, with an occasional patient harboring a streptococcus. He further demonstrated a bacterial inhibiting substance in human milk which was later identified as lysozyme by Rosenthal and Lieberman.<sup>12</sup> Blatt and Kessler<sup>13</sup> confirmed these observations. The immunologic implications of these studies as related to puerperal breast infections are suggestive.

Proper breast hygiene, therefore, must include control of such environmental factors as well as attention to the nipple. Miles and co-workers<sup>14</sup> showed that the nasal carrier rate of the *Staphylococcus aureus* in England averaged 47.4 per cent. A recent editorial in *Lancet*<sup>15</sup> suggested the use of penicillin as a spray or mist to the nose and throat of mothers and hospital attendants as a measure



and ninth months of gestation was encountered twice. Two infants, each one month of age, accounted for three more abscesses. Two of the abscesses evacuated themselves spontaneously, while one was incised. It is interesting that the infant with unilateral involvement was admitted with its mother who was also suffering from acute mastitis. Both were treated with intramuscular penicillin. While the mother's breast responded, the infant's failed to do so, and spontaneous evacuation of the pus occurred within twenty-four hours after admission.

In the puerperal mastitis group, 18 patients, when first seen, were suffering from abscess. Sixteen of the breasts required incision and drainage, while two cleared after aspiration. Forty-eight patients were treated with intramuscular penicillin during the cellulitis phase of the disease with complete resolution in each instance. This amazing response was reflected by the evident decrease in morbidity which averaged 6.1 hospital days. Recovery was complete. In contrast, the surgically treated group required 42.2 days from onset to complete healing.

*Dosage.*—Originally, treatment consisted of a total dosage of 840,000 Oxford units of penicillin. Twenty-five thousand Oxford units were given intramuscularly every three hours for seventy-two hours, and then 15,000 Oxford units every three hours for forty-eight hours. Symptomatically, all patients were well after sixty hours of treatment, but, because of the frequency of bacterial "persisters" in staphylococcal infections, it was felt wise to give the full five-day treatment. Penicillin blood levels taken one-half hour after administration averaged 0.371 Oxford units per milliliter. This was well above the optimum level of 0.156 required for staphylococcal infections.

Green, Burkhart, and Hobby<sup>7</sup> reported the presence of penicillin in 8 of 11 human milk samples. In contrast, Seeley and his group<sup>8</sup> failed to identify penicillin in cows' milk after intravenous administration of 500,000 Oxford units, and concluded that the bovine mammary gland was not permeable to penicillin. In the present study, 10 normal patients, used as controls, were given, intramuscularly, 300,000 Oxford units of penicillin in oil and wax. Under as aseptic precautions as possible, milk was obtained both before and eight and one-half hours after administration of penicillin. A sample of blood was obtained at the time of collection of the last milk specimen. Cultures and bacterial counts were performed on the milk specimens while both blood and milk samples were assayed for penicillin.

The results are detailed in the tables, and it is obvious that penicillin did not materially influence either the contaminating organism or the bacterial count. No penicillin was identified in any of the milk specimens. However, we were technically unable, using a variety of methods, to identify traces of penicillin in milk. The penicillin level in the blood eight and one-half hours after its administration was consistent with the results of Romansky and Rittman.<sup>14</sup> The beneficial effects from penicillin in the treatment of human puerperal breast infections are apparently due to the penicillin in the blood stream rather than that in the milk.

*Nursing State.*—In this series, breast infection was incident to weaning in 17 patients, while the remaining number were nursing their infants. When present, lactation was inhibited by the usual measures including the use of diethylstilbestrol in a total dosage of 40 milligrams. This plan was elected because of early experience with three patients in whom inhibition of lactation was not practiced. Each was treated with penicillin for a mild breast infection during the immediate postpartum period. The infection promptly cleared and they were encouraged to continue nursing their infants. About two weeks later each of the three patients developed acute mastitis in the contralateral

## Conclusions

1. Penicillin, if given sufficiently early, will prevent suppuration in acute staphylococcic puerperal mastitis.

2. Because penicillin is not secreted in the milk in sufficient amounts to control contaminating staphylococci, it is felt advisable to inhibit lactation to prevent reinfection of the breast.

3. Sulfonamide therapy is not recommended as a substitute for early penicillin therapy.

The bacteriologic work, including penicillin assays, was performed by Miss Edna Jackson of the Bacteriological Department, Division of Laboratories, Henry Ford Hospital, Detroit, Michigan.

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of control. Knott and Blaikley<sup>16</sup> have enforced this type of program for the past two years, and stated that the incidence of micrococcus carrier infections in the maternity ward was reduced 50 per cent by such spraying. Local penicillin to the nipples remains to be evaluated as an agent of merit. We have used penicillin ointment with some apparent benefit to cracked and fissured nipples, although the number of cases is too small to permit evaluation.

*Suppurative Mastitis.*—The distressing feature of a breast abscess is the prolonged morbidity, since the usual patient is under medical care for almost one and one-half months. In the present group of 18 cases of simple abscess, the time from onset to complete healing averaged 42.5 days. The tendency of the infected breast to develop secondary suppurative foci has long been recognized. Velpeau<sup>17</sup> in 1853 reported as many as 52 separate abscesses in one breast. He stated that the duration of illness depended upon the individual duration of each purulent formation. Penicillin can be expected to prevent this complication, and its administration is advised for those patients requiring surgical drainage. This opinion is shared by Power and Cravotta.<sup>5</sup> It has been the clinical impression in patients so treated that convalescence is shortened. Decrease in drainage, pain, and induration has been evident.

The limit of breast cellulitis is generally considered as being about forty-eight hours, and persistence of infection after that period of time usually results in suppuration. It has been our custom to give patients the benefit of a trial of penicillin therapy, regardless of the duration of symptoms, unless there was an area of softening indicating a localized abscess. Two patients who had evidence of infection for five and seven days, respectively, failed to show the expected response to the five-day plan of treatment. Aspiration on the fifth day yielded a small amount of pus from which was cultured *Staphylococcus aureus*. Because central softening of the mass could not be demonstrated, penicillin therapy was continued for five additional days with complete resolution. This type of case must be considered as borderline for penicillin therapy, and failure of the treatment can be expected in a certain number of instances due to errors in judgment.

*Sulfatherapy.*—The results obtained in this group of patients with sulfonamide therapy were disappointing. Five per cent sulfathiazole cream was used as a nipple dressing in many of these patients. It is apparent that it offered little protection. Before penicillin became available, 12 patients were treated during the cellulitis phase of the disease with various sulfonamides in apparently adequate dosage. Nine patients required incision and drainage of an abscess, giving a failure of 75 per cent. Four patients were admitted for penicillin treatment after having failed to respond to sulfadiazine. All promptly resolved when penicillin was given. One patient was admitted for incision and drainage of an appendiceal abscess. Six grams of sulfonamide were deposited into the abscess cavity, and sulfadiazine was continued orally, 1 Gm. every four hours. In the midst of this therapeutic program a breast infection developed on the seventh postoperative day. The more energetic action of penicillin appears to be required for this type of infection.

*Disadvantages of Penicillin Therapy.*—The main objections to penicillin therapy are required hospitalization, frequency of injections, and cost. Of the methods advocated for decreasing the frequency of injections, the oil and wax penicillin preparation of Romansky and Rittman<sup>18</sup> appears the most practical. Four patients in the present group have been treated with this preparation. One injection of 300,000 Oxford units was administered every second day until three doses had been given. The response was as satisfactory as could be expected from the multiple three hourly injection method herein described. Hospitalization was not necessary, and the cost was not prohibitive.

for the first week, there was no cause for anxiety during convalescence according to the author, who reported the case five months after operation and stated "the patient is learning to walk again, and there seems to be every prospect that she will make a complete recovery."

In 1933, Greenhill<sup>8</sup> reported a cystic fibroid weighing 47 pounds, and simulating an ovarian cyst which was removed at autopsy performed Oct. 24, 1928. He stated, "Because of the rarity of the occurrence of large uterine fibrocyts, the difficulty in making a correct clinical diagnosis, and the relatively large number of deaths which occur without operation due to disturbances in circulation, breathing, and cachexia, I am reporting this case." The patient was a 48-year-old Negro nulligravida, upon whom paracentesis has been performed about seventy-five times during the last year. Menses ceased four months prior to admittance to Cook County Hospital, and the patient had been free from menstrual disturbances. Her condition was so grave that operation could not be performed.

### Report of a 55-Pound Myoma

Mrs. M. L. M., T-43-59162, born in New Orleans June 6, 1883, of Spanish parents, was admitted to the hospital on Aug. 15, 1942, complaining of "swelling of the stomach," inability to walk, orthopnea, marked weakness, etc. During the summer of 1925 she first noticed a mass "about the size of an orange" in the lower abdomen.

In 1932 the tumor had reached the umbilicus and a visit was made to the office of the mother's physician, who advised surgery. The patient declined as she "thought operation would mean death;" furthermore, she was free from pain and uterine bleeding. During the next ten years her health continued to be "good," and she performed all of her household duties, even though the tumor became larger and larger. However, in July, 1942, the mass had assumed such proportions that she was mechanically incapacitated. On Aug. 1, she became bedfast and complained of marked weakness. Upon being seen at home by one of us (H. T. B.), she bemoaned the fact that her abdomen was "bigger than the rest of the body," and she firmly believed that an early death was inevitable. She consented to be hospitalized.

Interrogation revealed that the menses began at the age of 11 years, occurred regularly and normally without pain every twenty-eight days, lasting five days, and finally disappeared at the age of 42 years. There were no known pregnancies. The tumor was first noticed shortly after the cessation of her last menstrual flow.

Review of systems revealed the following positive findings: loss of adipose tissue, progressive for four years; night sweats without known nocturnal fever; palpitation at times; dyspnea which had increased to the stage of orthopnea; dependent edema for "at least four or five months"; chronic constipation, partially relieved by mineral oil. The urinary index was not abnormal, nor were there any urinary symptoms.

Past history disclosed no previous hospitalizations or serious injuries. The family history revealed no evidence of neoplasia.

Upon admission to the hospital, the following data were obtained: temperature 100.6° F., pulse 100, respiration 30, weight 145 pounds, height 56 inches, circumference of abdomen 51½ inches, and blood pressure 130/78. The patient had an abdominal enlargement to such a degree that she could not stand alone. Emaciation was marked. The skin of the abdomen and lower extremities was under great tension due to swelling. The mucous membranes were pale. The thorax was bilaterally symmetrical with an upward and outward displacement

## A 55-POUND SOLID UTERINE MYOMA\*

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ON JAN. 3, 1888, Hill<sup>1</sup> successfully removed a 47-pound fibroid. On Dec. 16, 1902, Webster<sup>2</sup> surgically obtained an 87-pound cystic myoma with survival of the patient.

On July 30, 1906, Cullen<sup>3</sup> successfully extirpated an 89-pound cystic myoma. Reporting the case eight months after operation, he stated that the 58-year-old patient "is in perfect health and is gaining rapidly in weight." He said that she had noticed the tumor for twenty years, and that she was delivered of a healthy baby about eighteen years prior to operation. Although suffering from the large abdominal tumor, she was able to do her work until three weeks before being referred to Cullen. Her chief inconvenience had been her inability to lie on her back in bed, "and sometimes when she would get stalled, it was necessary for her husband to turn her over quickly, otherwise, she would have suffocated." Upon making an incision over the most prominent part of the tumor with the patient in a sitting position and under ether anesthesia, an attempt to puncture it proved unsuccessful. Bleeding occurred, thereupon the incision was enlarged to the xiphoid process and the tumor removed in toto. Within eight hours after operation the temperature rose to 102.2° F. but dropped to 100° F. by evening. The highest pulse rate was 130. Postoperative vomiting is said to have been absent. The legs were bandaged on account of the edema. Catheterization was required only once. On the fourteenth day diarrhea caused considerable discomfort and "persisted off and on for a couple of weeks. At this time, however, the weather was excessively hot, and diarrhea was general throughout the hospital," he wrote. Twenty-three days after operation the patient weighed 80½ pounds, in comparison to the 174 pounds which she weighed upon admission. The pathologic description included, "the growth is, however, evidently made up of one large cystic state and numerous smaller ones together with the semisolid area." Kelly and Cullen,<sup>4</sup> in their excellent book on uterine myomas, considered this case to be the largest authentic successful one on record.

In 1923, Farmer<sup>5</sup> reported recovery after removal of a 35-pound tumor. The following year Marshall<sup>6</sup> successfully removed a 47-pound myoma. On May 26, 1925, Stevens<sup>7</sup> extirpated a uterine fibromyoma weighing 47 pounds, 5 ounces. The patient, aged 59 years, had five children, and had reached the menopause at 49 years "after some years of severe menorrhagia." She knew that she had had the tumor for twenty years. The operation was performed under chloroform anesthesia, using a block and tackle of which a photograph is shown in Stevens' article. The incision was about eighteen inches long and the "tumor was almost spherical in shape and contained a few small cystic cavities without other important degenerative changes." "The day after operation the respirations rose to forty per minute without any rise in temperature and without bronchitis or other lung complications." Other than this very rapid breathing

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displaced. The uterus could not be outlined, nor were the ovaries palpable. External hemorrhoids were present. The mass eneroached upon the anterior wall of the rectum.

On admission, the urine presented the following findings: alkaline, specific gravity 1.015, 2 plus indican, a trace of albumin, innumerable leucocytes, and many Gram-negative bacilli. Four days later there had been a marked decrease in the number of leucocytes present. On the day of admission the hemogram was: hemoglobin 55 per cent, erythrocytes 4,700,000, leucocytes 29,250, with 90 per cent polymorphonuclear neutrophils. Platelets, coagulation, bleeding, and blood sedimentation rates were essentially normal. On the second day after admission, urea nitrogen 8.9 mg. per 100 c.c. of blood, sugar 111, ehlorides 976, and serum proteins 6.16 Gm. Blood Kline and Kolmer tests were negative.

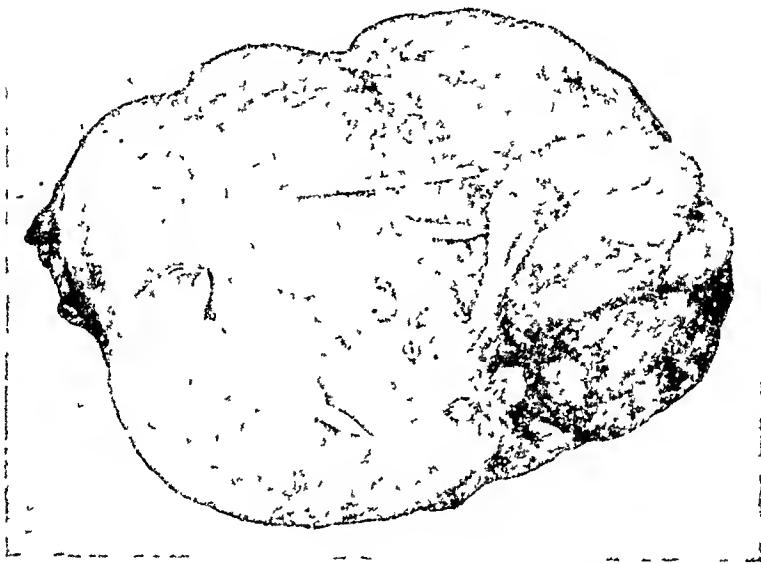


Fig. 2.—Tumor weighed 55 pounds. Note the six-inch rule.

A high calorie, vitamin rich diet was begun on admission. An indwelling urethral catheter was inserted, and sulfathiazole was given to combat urinary tract infection. The patient received blood transfusions and supplementary fluids in the form of 10 per cent dextrose in water. Mild laxatives and enemas were required. Seconal, morphine sulfate and scopolamine were given pre-operatively.

Upon arrival of the patient in the operating room, with the urethral catheter in place, an infusion was begun through a No. 17 gauge needle. The skin was prepared with ether and tincture of merthiolate. A short infraumbilical incision was made under procaine infiltration anesthesia. Exploration ruled out the possibility of the huge mass being a cyst. The patient was then anesthetized with cyclopropane, and a blood transfusion was begun. The incision was extended to the xiphoid process and the symphysis pubis. Every accessible blood vessel to and from the tumor was clamped, severed, and ligated with catgut. The greatly distorted bladder was retracted near the symphysis pubis. The right ureter measured about 2.5 cm. in diameter. Multiple adhesions were freed. The appendix appeared grossly normal. The left ureter was dilated less than the right. It was possible to clamp across the vaginal vault and remove the tumor in toto. The blood pressure fell to 60/40, and the pulse

of the lower ribs. The xiphoid process was displaced cephalad. Atrophy of the mammary glands was such that they hung as folds of skin. Moist râles were audible over the lung bases. The heart was displaced laterally. The peripheral arteries exhibited evidence of sclerosis.

An asymptomatic umbilical hernia was present. The superficial blood vessels were plainly visible. There was no evidence of free fluid in the abdomen.

The labia majora and minora showed evidences of atrophy. The vaginal introitus admitted the smallest Graves' speculum. Senile changes were present. The cervix uteri could not be palpated, as it had been drawn up by the pelvo-abdominal tumor. The hard nontender mass filled the pelvis and could not be



FIG. 1.—A, Aug. 21, 1942, patient too weak to stand alone. Weight, 145 pounds. B, One month postoperatively she weighed 70 pounds.



Following a pressure dressing, two sand bags were applied. The operating time was sixty-five minutes. The blood pressure was 100/65 at the end of the procedure.

The pathologist, Dr. Emma Moss, reported as follows: The specimen consisted of a huge mass, weighing 55 pounds and being 17 inches in its greatest diameter. It had been bisected, and was solid except for a few very small cystic areas filled with a light yellow to reddish fluid. In many areas it showed evidences of degeneration. It presented a general appearance of having been encapsulated. A tube and somewhat cystic ovary could be identified. The opposite ovary was thinned out by the mass to such an extent that only a prolonged remnant remained. One surface of the uterus could be identified, and it evidently was the site of origin of the tumor. The outer surface was smooth and red. Final corrected microscopic diagnosis: "Leiomyoma with degeneration. Acute and chronic inflammation. No evidence of malignancy."

After the first four uneventful postoperative hours, the blood pressure suddenly dropped to 90/60, and 500 c.c. of citrated blood were administered to supplement the 1,000 c.c. received on the operating table. After two hours the blood pressure returned to a satisfactory level. Intravenous fluids were administered. Wangensteen suction was employed for the first two days. After twenty-four hours the sand bags were removed from the abdomen. On the third postoperative day the patient was afebrile, with a soft abdomen, and appeared clinically much improved.

On the fifth postoperative day the patient received 500 c.c. of plasma during the morning, after her serum protein was found to be 4.4. That night, after having received 250 c.c. of plasma, she experienced a chill with temperature going to 105° F., the pulse rate to 140 per minute, and the blood pressure dropped to 50/30. Adrenalin, morphine, and oxygen were administered. She was dyspneic, cyanotic, and unconscious, with râles in her lungs. Digalen was begun. Roentgenography revealed cardiac enlargement and passive congestion of both lungs. Electrocardiography revealed low amplitude of complexes compatible with congestive failure.

The following day the patient developed diarrhea. No evidence of eul-de-sac infection was found. Studies of the stool revealed atypical Shiga paratyphoid and atypical Salmonella paratyphi. The urine contained numerous blood cells. The patient's condition gradually improved. On the eleventh postoperative day, after all sutures had been removed and an abdominal binder had been applied, the patient was allowed up in a wheel chair.

On the twenty-fifth postoperative day the patient weighed 70 pounds, and she was able to walk with assistance. One week later she was discharged, free of edema, and weighing 75½ pounds. Six months later she weighed 124 pounds. The circumference of the abdomen was 34 inches.

When last seen (Jan. 23, 1947) she was in excellent physical condition for the age of 63 years.

### Summary and Conclusions

1. The history of uterine myomas constitutes one of the most fascinating chapters in the story of gynecology.

2. Successful removal of uterine myomas weighing more than 25 pounds has been authentically reported by Hill,<sup>1</sup> Webster,<sup>2</sup> Cullen,<sup>3</sup> Farmer,<sup>5</sup> Marshall,<sup>6</sup> and Stevens.<sup>7</sup> The tumors in the cases of Webster<sup>2</sup> and Cullen<sup>3</sup> weighed 87 and 89 pounds, respectively, and were cystic.

3. The solid myoma in the case herewith reported weighed 55 pounds and measured 17 inches in diameter. The patient is enjoying excellent health four years after operation.



increased to 135; however, the patient responded to ephedrine sulfate and increased rate of administration of blood.

The raw area exposed was tremendous. The kidneys, liver, spleen, stomach, and intestines had been markedly displaced upward, and showed the effects of pressure. Hot packs were used to control oozing from the areas which could not be sutured or ligated. Fortunately, sufficient peritoneum had been removed from the tumor to permit very satisfactory covering of denuded areas. The peritoneum and fascia were closed with four sutures of chromic catgut. Six tension sutures of silkworm gut were employed. The skin was sutured interruptedly.



Fig. 2.—Six months postoperatively. Patient weighed 124 pounds.

## LEIOMYOFIBROMA OF THE UTERUS AND ENDOMETRIAL CARCINOMA\*

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A NUMBER of statements in the literature refer to the frequent occurrence of leiomyofibroma of the uterus with endometrial carcinoma of the uterine body. Considerable importance has been ascribed to this association, not only in regard to certain clinical considerations in affected patients, but also as indicating a possible etiologic relationship between the conditions. On the other hand, a few authors have expressed skepticism regarding any real significance to be found in the coexistence of the tumors. Several have even doubted any connection whatsoever between the two, and, among other points, have made mention of the clinical impression that fibroids of the uterus are frequently present without, as well as with, endometrial carcinoma. However, actual statistical facts regarding this controversial matter seem to be largely lacking.

Forty-five years ago Cullen<sup>1</sup> noted that a large percentage of his cases with carcinoma of the uterine body also had fibromyomas. However, he stated that myomas were so common that the high incidence here was not surprising. Meigs,<sup>2</sup> in addition to citing statistics from the literature, gave the occurrence of uterine fibroids with endometrial carcinoma at the Massachusetts General Hospital as 20.8 per cent. Other reports on the coexistence of fibroids with carcinoma give such high percentages as 34.9 by Norris and Dunn;<sup>3</sup> 38, Healy and Brown;<sup>4</sup> 36.4, Masson and Gregg;<sup>5</sup> and 37.8 by Scheffey, Thudium, and Farrell.<sup>6</sup> From the other point of view, that is, regarding the incidence of carcinoma among fibroid uteri, the statistics, though considered significant, are not so striking. For example, in 1909 Kelly and Cullen,<sup>7</sup> among 1,400 myomatous uteri, found 25 or 1.7 per cent to have corpus carcinoma also. Figures given by other authors all remained within the vicinity of 1 or 2 per cent, except for the surprisingly high percentage of 9.9 in a small series reported by Falls.<sup>8</sup>

An important clinical feature of the frequent coexistence of fibroids and endometrial carcinoma was indicated by Scheffey, Thudium, and Farrell<sup>6</sup> when they stated that too often menorrhagia and metrorrhagia were ascribed to the presence of the fibroids with consequent disregard of the malignancy possibility. Also, the frequent coexistence of fibroids would seem greatly to affect the accuracy of attempts at estimating the extent of the malignant growth on the basis of the size of the uterus, as suggested by Healy and Brown.<sup>4</sup> Of interest in another direction is the fact that the frequent finding of uterine myomas with endometrial carcinoma has led to considerable speculation regarding some etiologic connection between the two. Meigs,<sup>2</sup> granting the possibility that the presence of fibromyomas might lead to carcinoma, believed, however, that the association was more likely due to the ability of some uteri to develop malignant as well as benign tumors. To Novak,<sup>9</sup> although agreeing in general with Meigs,

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leaves 574, or 25.5 per cent, entirely free of fibroids, or at least without tumors of sufficient clinical importance or size to justify mention.

Included in the 2,246 hysterectomy cases were 44 in which carcinoma of the uterine body was present. (It should be noted that during the same five years at Harper Hospital there were 74 other cases of endometrial carcinoma, in which, however, hysterectomy was not done; but for various reasons [chiefly for hopelessly advanced disease] treatment was confined to irradiation therapy, or in a few instances to diagnosis only. These cases were not included in the studied series since knowledge of the presence or not of fibroids was dependent on ordinary pelvic examination, and was therefore far too subject to error for accurate statistical study.) These 44 cases treated by hysterectomy had for the most part also received preliminary irradiation, but, as this had been done within two months of operation in the vast majority, it could have had insufficient time for much effect on the size of fibroids where these were present. Finally, it is pointed out that the figures given here are very questionable as an indication of the actual incidence of endometrial carcinoma, but they are presented only as probably of considerable value in suggesting the relative occurrences with and without fibroids.

TABLE I. A FIVE-YEAR SERIES OF ABDOMINAL HYSTERECTOMIES SHOWING THE INCIDENCE OF ENDOMETRIAL CARCINOMA AMONG UTERI WITH FIBROMAS AND IN THOSE WITHOUT THESE TUMORS

	ALL CASES	WITH FIBROMAS	WITHOUT FIBROMAS
Hysterectomies	2,246	1,672	574
With endometrial carcinoma	44	15	29
Percentages	2.0	0.9	5.1

In Table I it is seen that the 44 instances of corpus carcinoma among 2,246 hysterectomies give an incidence of 2 per cent. For the 1,672 uteri with the diagnosis of fibromyoma, the occurrence of carcinoma was 15, or 0.9 per cent. This latter figure agrees fairly well (except for Falls's small series) with previous reports as given above in the discussion of the literature. However, among the 574 uteri of the series without leiomyofibromata, there were 29, or 5.1 per cent, with carcinoma of the endometrium. It is such comparisons which strangely seem to be lacking.

Since the foregoing findings were so contrary to what was to be expected from statements in the literature, a comparison in another direction seemed indicated as a check. For this purpose a group of uteri from patients with endometrial carcinoma was contrasted with another series of the same size which was comparable as to age and other factors, except that uterine malignancy was absent. Having some resemblance to this was a comparison by Meigs<sup>2</sup> of cases with uterine cervix carcinoma and others with carcinoma of the corpus. His study apparently showed a greater affinity of the latter for myomatous uteri since the ratio of carcinoma of the body to that of the cervix was increased from 1 to 3.7 in general occurrence to 1 to 2 in cases with fibroid uterus. However, such an important factor in the incidence of fibroids as the ages of the members of the groups was apparently not considered. Moreover, it is not clear

it also seemed logical to suppose that an irritative effect of fibroids, especially the submucous variety, might produce some predisposition to endometrial malignancy.

Recently, with the great interest in endocrinology, there has been considerable conjecture regarding an explanation of the frequent association of the growths on the basis of a common etiologic factor in the nature of internal glandular dysfunction. Particularly mentioned as a possibility has been excessive estrogen effect. In support of the fibromyoma side of the picture, much has been said regarding the work of Nelson<sup>10</sup> and others in the experimental production of fibroid uterine nodules in animals by abnormally high or unopposed estrogenic effect. Interesting as may be the possibilities of these experiments, it should be remembered that the artificially produced nodules have only some resemblances to fibromyomas and are not complete duplicates.<sup>11</sup> Moreover, there appears as yet to be no unequivocal or clear-cut experimental, clinical, or statistical evidence favoring a speculative connection between estrogenic action and uterine fibroids as found in women. Consequently, the frequent finding of fibromyomas with endometrial carcinoma cannot as yet be considered reliable support for the rather commonly believed in, but still largely hypothetical, estrogenic etiology of the latter condition.

The foregoing is far from a complete survey of the literature on the subject of uterine fibromyomas and endometrial carcinoma, but it does give some illustrative examples of the extensive speculation and investigation which have been devoted to the connection between the two growths. After critically reviewing this material, interesting and thought provoking as it may be, it appears that one might well inquire as to why all this theoretical work has been undertaken when one fundamentally basic fact seems as yet not to have been established. I refer to the lack of good and substantial evidence that carcinoma of the uterine body has a disproportionately higher incidence among fibromatous than among the nonfibroid uteri of a series of cases. Or, looked at from the other direction, one searches in vain for satisfactory proof that fibromyomas, though admittedly frequently associated with endometrial carcinoma, are in fact more often found with that growth than in instances, comparable as to age and other factors, where it is not present. Actually, there is a remarkable dearth of studies regarding the point. Having some bearing on the matter were certain data which we obtained incidentally in the investigation<sup>12</sup> of another subject, and which failed to suggest any increased incidence of leiomyofibroma with endometrial carcinoma. Because of small numbers, however, as well as other reasons, definite conclusions could not be drawn, and a more extensive examination seemed indicated. Consequently, a study was made of a substantial series of cases with hysterectomy from Harper Hospital.

At this hospital during the five years from 1939 through 1943 there were 2,246 abdominal hysterectomies which were done on various indications. Of this number, there were 1,389 with fibromyoma as a primary diagnosis, either alone or in combination with other conditions. Presumably in these cases the tumors were of definite clinical significance because of size, abnormal bleeding, pressure symptoms, or for other reasons. There were an additional 283 in which fibroids were mentioned in the secondary diagnosis. Together, then, there were 1,672 myomatous uteri, or 74.5 per cent of the entire series of 2,246. This

tainly offer no evidence favoring the idea of a connection between fibromas and carcinoma of the uterine body, but rather just the opposite.

### Summary

The frequent coexistence of fibromyomas of the uterus and endometrial carcinoma has been the subject of considerable conjecture and investigation regarding its significance from both clinical and etiologic standpoints. It has never been satisfactorily established, however, that the high incidence of fibroids can be considered as peculiar to or characteristic of corpus carcinoma, and not just simply a reflection of the frequent occurrence of fibromyomas. In order to remedy the surprising dearth of information on this essential and basic point, a study was made of hysterectomies at Harper Hospital. Among 2,246 consecutive abdominal hysterectomy cases there were 44 with endometrial carcinoma, an incidence of 2 per cent. In this series there were 1,672 with a diagnosis (1,389 primary and 283 secondary) of fibromyomas, of which only 15, or 0.9 per cent, showed carcinoma. In marked contrast, the group of 574 without fibroids had an incidence of 29, or 5.1 per cent, with uterine fundus cancer. As a check on this unexpected finding, a series of 50 endometrial carcinoma cases were compared with a like number of noncancerous instances, falling into the same age groups, and in whom the operations had been done for various reasons other than fibromyomas. Of the carcinomatous uteri there were 18 with fibroids, while in the other group the number was 23. There is no evidence in these data to indicate that fibromyomas of the uterus and endometrial carcinoma have an affinity for each other, but rather the reverse.

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whether or not the groups were compared on the basis of data obtained from ordinary pelvic palpation or by accurate examination of excised organs. In the present study the previously used 44 instances of endometrial carcinoma treated by hysterectomy were increased to 50 by the addition of 6 similar cases from the complete year 1938 and the first 2 months of 1944. According to age the 50 women fell into ten-year groups as follows: 30 to 39 years, 2; 40 to 49 years, 13; 50 to 59 years, 23; and 60 years and over, 12.

The 50 cases for contrast with the endometrial carcinoma series were found after a search through the abdominal hysterectomy records for the five-year period 1939 through 1943, plus approximately the first half of 1944. In order that there could be no question of padding, so to speak, of this group with a disproportionate number of fibromyomatous cases, only those instances were included in which the uteri were removed for reasons *other* than fibroids. Actually, the indications were as follows: pelvic relaxation, malposition, etc., 16; ovarian tumors—malignant, 9, and benign, 3; pelvic inflammatory disease, 9; functional bleeding, 6; unexplained postmenopausal bleeding, 3; endometrial polyp, 3; and adenomatous polyp of the cervix, 1. In addition to comparable ages for the two groups, there was also a rather close correspondence in other respects. For example, in the carcinoma group 47 were married and 36 of these gave a history of one or more pregnancies; whereas, in the other series the figures were 48 and 39 respectively. Again, of the 50 women with carcinoma, there were 16 who were, or at least considered themselves to be, still menstruating; while in the other group there were 19. It is perhaps worthy of mention that there was no necessity to take into consideration the influence of race, since all but 3 of the 100 women in the two groups were Caucasians.

TABLE II. OCCURRENCE OF FIBROIDS IN 50 UTERI WITH ENDOMETRIAL CARCINOMA AND A SIMILAR GROUP OF CASES AS TO AGE, ETC., WITHOUT CANCER OF THE UTERINE FUNDUS

	WITH FIBROIDS			
	SMALL	(SIZE OF 12 TO 16 WEEKS' PREGNANCY)	LARGE	TOTAL
50 with endometrial carcinoma	14	2	2	18 (36%)
50 without endometrial carcinoma	17	4	2	23 (46%)

In Table II is the comparison of the two groups showing the number of fibroid and nonfibroid uteri. The former are further analyzed roughly as to size of the tumors, the estimations being based on statements of the operators and measurements taken in the laboratory. In every instance there is a fairly close agreement between the two series, rather than an increased incidence of fibromyomas for the cancer group, as might be expected from certain statements in the literature. Indeed, it is slightly higher for the noncancer cases. This fact assumes greater significance when it is recalled that in the latter group the indications for hysterectomy were conditions *other* than fibromyomas in all instances. These data largely confirm the results of the first comparison, and cer-

classifiable as hypertensive toxemia. While there must have been many more cases, we have taken only those in whom (a) hypertension was known to have existed before pregnancy, or (b) hypertension was found before the twenty-fourth week of gestation, no previous normal readings having been recorded during the pregnancy. Our standard for hypertension is 140/90 or greater. Patients showing hypertensive levels of blood pressure only at the initial clinic visit were excluded. Recognizable cases of glomerulonephritis and pyelonephritis were rejected; however, 15 patients (7 per cent of the series) were classifiable as renal disease. We believe that these are cases either of nephrosclerosis secondary to the hypertensive disease, or with superimposed pre-eclampsia.

Our postpartum toxemia clinic records have been of great value, in that they have given us repeated blood pressure readings while the patients were not pregnant. We recently have looked through the record room files of every hospital in Hudson County, and whenever we found an admission of one of our patients, before or after she came into our hands, we have studied her hospital chart.

At follow-up, we have determined the blood pressure, by mercury sphygmomanometer, with the patient sitting, and (usually) again, after examination and quiet reassurance, with the patient lying down. The lower reading is reported. The diastolic pressure was taken as the point at which the pulse sounds suddenly became dull and muffled. The eye grounds were examined without mydriasis. A palpatory estimation was made of the state of the radial arteries, and the heart was auscultated. Cardiac size was determined by x-ray. The morning urine was examined for protein, sugar, specific gravity, and formed elements. Unless the specific gravity of protein and sugar-free urines exceeded 1.022, urea clearances were done. Blood chemical determinations included sugar, nonprotein nitrogen, and urea.

### The Hazards of Pregnancy

Since a detailed analysis of the 301 pregnancies was published in the March issue of this JOURNAL, we shall merely summarize our findings, which are in general agreement with the reports of others.

Nearly 40 per cent of our patients showed significant drops in the mid-pregnancy blood pressure. Often the pressure fell into the normal range. About half of the patients went through the entire pregnancy with essentially constant blood pressures. Near delivery, the blood pressure was increased over the initial levels in 30 per cent of cases.

The outstanding hazard of pregnancy is the superimposition of toxemia, which occurred in about 30 per cent (by our criteria: increase in blood pressure and appearance of proteinuria, or marked proteinuria alone, or edema in combination with either of the above or toxic symptoms). The incidence of eclampsia in these hypertensives was exactly 10 times that in all patients, while the incidence of pre-eclampsia was increased seven times. We could find no satisfactory criteria by which to judge the likelihood of toxemia occurring. It is somewhat more common in young primiparas, and has a recurrence rate of close to 70 per cent in later pregnancies. Its incidence bears no relation to the severity of the original hypertension.

There were six immediate maternal mortalities, four of which occurred in the first pregnancy definitely classifiable as hypertensive. In addition, seven women died within the first four months post partum. These 13 deaths give a maternal death rate of 4.3 per cent, or 20 times that for all patients in this clinic. Two of the deaths followed abortion—one therapeutic and one spon-



## Original Communications

### A STUDY OF THE INTER-ACTION OF PREGNANCY AND HYPERTENSIVE DISEASE\*

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WHILE there have been several studies of the effect of hypertensive disease upon pregnancy, there seems to be but little known of the effect of pregnancy upon the hypertensive disease. It is recognized that pregnancy is immediately hazardous to the hypertensive woman and to her fetus, and it has been surmized that once through the pregnancy, the mother has suffered irreparable damage which shortens her life expectancy. This supposition does not appear to be buttressed by solid evidence.

In the present paper, we shall report our findings in all patients aborting or delivering in this hospital, in whom the diagnosis of hypertensive disease could be established from blood pressures recorded before the twenty-fourth week of gestation. The fact that therapeutic abortion was done in only three of the 301 pregnancies gives us an almost unique opportunity for studying the interaction of pregnancy and hypertensive disease. In the follow-up of patients, we have traced every patient to 1946.

Stander and Peckham<sup>11</sup> followed up 57 per cent of their patients who were diagnosed as having "nephritis complicating pregnancy," and found a mortality of 40 per cent among those traced. While they felt that pregnancy had aggravated the disease and hastened the end, they were unable to prove this. Browne and Dodds<sup>12</sup> followed 65 patients with hypertensive disease, and came to the conclusion that the large majority could pass through several pregnancies successfully and without any demonstrable deterioration in their condition. Reid and Teel,<sup>10</sup> in studying 122 patients with hypertensive disease, could not "find enough evidence to justify radical interference in patients already pregnant, with mild asymptomatic hypertension, normal hearts and kidneys." Wellen, Welsh, and Taylor<sup>15</sup> followed six women with hypertensive disease through seven pregnancies, and for periods up to four years post partum. They found no evidence that pregnancy had any deleterious effect as judged from blood pressure, renal blood flow, or diodrast Tm (normal tubal excretory capacity).

#### Material and Methods

We have searched through all charts bearing the diagnosis of "toxemia of pregnancy," covering the period from the opening of the hospital in October, 1931, through 1944. There were 218 patients seen here in 301 pregnancies

\*The Prize Award Thesis, presented at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

The causes of death, ascertained from hospital charts in 34 cases, and from death certificates in five, may be summarized as follows: Cerebral accident, 13; cardiac failure, 9; renal failure, 5; toxemia of pregnancy, 2; sudden death, 2 (ascribed to myocardial failure in the death certificates); and intercurrent, 8.

TABLE I. SUMMARY OF FOLLOW-UP FINDINGS IN 218 HYPERTENSIVE WOMEN

INITIAL SYSTOLIC BLOOD PRESSURE, MM. HG	140 TO 159	160 TO 179	180 TO 199	200 OR MORE	TOTALS
Cases	89	71	29	29	218
Dead, per cent	13.5	11.3	20.8	48.3	17.9
Annual death rate, per thousand	17.03		23.26	80.00	24.62
Percentage with aggravated hyper- tension at follow-up	46.4	30.3	28.6	26.1	36.3
Subsequent pregnancies, after orig- inal diagnosis of hypertensive disease (first year deaths ex- cluded)	42.5	38.8	46.4	29.2	40.3

Four of the intercurrent deaths were associated with pregnancy. One committed suicide four years after her second hypertensive pregnancy, one died of tuberculosis five and one-third years post partum, and two died of acute rheumatic endocarditis at three months and ten months after delivery, respectively. Thus 77 per cent of the deaths were associated with hypertensive disease (counting the sudden deaths as such).

The annual death rate, excluding the four immediate mortalities, was 24.62 per thousand, which is six times the expected rate for unselected urban women of the same age, color, and calendar year distribution.

Mortality tables were constructed exactly as outlined by Frost,<sup>8</sup> with the exception that patients dying during a given year were recorded as having a full year's exposure. For comparison, we have used the Metropolitan Life Insurance Company's data on mortality among virtually unselected women insured on the weekly premium paying basis.

The death rates among our hypertensive women show no significant increase with age, in the age groups covered by this study. The ratio of actual to expected deaths, in fact, decreases with age—the older women seem to withstand the disease somewhat better than do the younger ones (Table III).

TABLE II. REMOTE MORTALITY IN HYPERTENSIVE WOMEN\*

AGE AT DE- LIVERY	20 TO 24		24 TO 29		30 TO 34		35 TO 39		40 TO 44		TOTALS		
YEARS OF FOLLOW-UP FROM DE- LIVERY OF FIRST KNOWN HYPERTEN- SIVE PREGNANCY	PATIENT-YEARS EXPOSURE	DEATHS	PATIENT-YEARS EXPOSURE	DEATHS	PATIENT-YEARS EXPOSURE	DEATHS	PATIENT-YEARS EXPOSURE	DEATHS	PATIENT-YEARS EXPOSURE	DEATHS	PATIENT-YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000
1	20.0	0	60.0	1	46.0	4	57.0	1	30.0	1	213.0	7	32.86
2	19.5	0	57.5	2	41.5	1	53.5	1	29.0	0	201.0	4	19.90
3	19.0	1	53.5	2	38.5	0	47.5	0	26.5	0	185.0	3	16.22
4 to 6	41.0	1	120.0	1	94.0	1	119.0	2	52.0	3	426.0	8	18.77
7 to 9	21.0	2	79.5	1	66.5	2	76.5	3	27.5	0	271.0	8	29.52
10 to 12	7.0	0	25.0	0	30.5	3	26.0	1	20.0	0	108.5	4	36.36
13 to 14	1.0	0	5.0	0	2.0	0	3.0	0	3.5	0	14.5	0	0.0
Totals	128.5	4	400.5	7	319.0	11	382.5	8	188.5	4	1419.0	34	23.96

\*Follow-up reckoned from time of delivery of first pregnancy in which diagnosis of hypertensive disease was established. Omitted: Four immediate maternal mortalities, and the case of a 16-year-old girl who died two and one-half years after delivery.

taneous. Of the 13 deaths, eight were attributable to hypertensive disease, and five were chargeable to intercurrent causes.

The gross fetal loss in the 301 pregnancies was 38.2 per cent. In the 840 pregnancies occurring before the establishment of the diagnosis of hypertensive disease, the fetal loss had been 34.7 per cent. In 127 later pregnancies, it was 40.2 per cent.

The fetal mortality increased with increasing severity of the hypertension, with the appearance of proteinuria, with renal impairment, and especially with the superimposition of pre-eclampsia or eclampsia.

These data certainly establish the dangers of pregnancy itself—one woman in 23 died, and two in five lost their babies. Yet the majority of hypertensive women apparently are not jeopardized by pregnancy. Two thirds of our patients escaped superimposed toxemia. In this group, there were no immediate maternal deaths, and one of the two late puerperal deaths was of intercurrent causation. The fetal loss was 18.5 per cent. Among the one-third of patients who had pregnancies complicated by pre-eclampsia or eclampsia, there were six immediate maternal deaths (6.67 per cent), and five late puerperal deaths, giving a total maternal mortality of 12.2 per cent—10 times that in the uncomplicated hypertensive group. The fetal loss was exactly 50 per cent—almost three times that in the women who escaped superimposed toxemia. The follow-up findings to be presented indicate that repeated pregnancies are not remotely harmful to hypertensive women unless pre-eclampsia or eclampsia supervene.

If only we could determine which patients would escape superimposed toxemia, a good prognosis for pregnancy could be offered to two out of three hypertensive women. It is possible that the prompt termination of a hypertensive pregnancy at the first sign of developing toxemia would protect the patient from the dire possibilities which such toxemia carries. If this were so, then perhaps any hypertensive woman could be given a chance at pregnancy, should she desire it. While her risks would be greater than those of a normal woman, there is a good chance that close supervision might give her the baby she wants.

### Remote Mortality

Of the whole series of 218 cases, with *every patient* traced to late 1945 or 1946, 39, or 17.9 per cent, are dead. The length of follow-up varied from one to fourteen years, and averaged almost exactly seven years. Included in these 39 deaths are the six immediate and seven late puerperal deaths. Two of the immediate deaths will be considered as "remote" because they were associated with pregnancies subsequent to the one in which the diagnosis of hypertensive disease was established. All of the late puerperal deaths will be treated as remote, making 35 remote and 4 immediate fatalities.

The average age at death was 35.4 years; the ages ranged from 18 to 47 years. Of the 82 patients who had superimposed eclampsia or pre-eclampsia in 90 pregnancies, 26, or 31.7 per cent, are dead. In contrast, of the 136 patients who did not have superimposed toxemia, 13, or 9.6 per cent, are dead. The annual remote death rates were, respectively, 43.25 and 14.24 per thousand. For patients whose first observed blood pressure was 200 mm. Hg. or more, the annual death rate was 80.00 in contrast to 18.08 in patients whose initial pressures were less than 200. As for the 15 patients classified as having renal disease, 8, or 53 per cent, are dead (five of renal failure and three of cerebral hemorrhage). Urea clearances were done at follow-up in the seven survivors. Three clearances were less than 60 per cent, while four were 70 per cent or higher.

The death rate is highest in the first year post partum, because of the late puerperal mortalities. After the sixth year of follow-up, the death rate again increases (Table II).

*The Effect of Repeated Pregnancies.*—The patients were divided into three groups:

A. Those who have had no pregnancy subsequent to the one in which the diagnosis of hypertensive disease was established.

B. Those who had one later pregnancy, and

C. Those who had two or more later pregnancies.

Table III shows that the annual death rate is not affected by repeated pregnancies, even with the risk of superimposed toxemia in the later pregnancies. Admittedly, the women having later pregnancies may be a select group. We have, therefore, sought in various ways to correct for this factor of selection.

As a first approach, we have excluded first year deaths in making a separate calculation of the death rates in women having no later pregnancy (Table III). Thus all the cases represented in this column of the table have survived for at least a full year after delivery.

A direct method of determining the effect of later pregnancy is to calculate the death rates based upon periods of follow-up from the second, third, and fourth pregnancies, rather than from the delivery of the first known hypertensive pregnancy (Table IV). Inherently, however, the effect of this method is to retain all of the deaths, while shortening considerably the follow-up periods. That is, the more pregnancies the patients have, the higher the calculated death rates will be. Also, such calculation deals with women who are getting older, and who have had their hypertensive disease longer. Despite this stacking of the cards against the apparent conclusion to be drawn from Table III, we again find that repeated pregnancies have not increased the annual death rates. The patients with three or more pregnancies are so few that the death rate shown in line 12 of Table IV cannot be considered reliable, especially since one of the deaths was intercurrent.

TABLE IV. REMOTE MORTALITY RATES IN HYPERTENSIVE WOMEN HAVING REPEATED PREGNANCIES\*

	PATIENT-YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000
1. No later pregnancy	824.0	24	29.14
2. Later pregnancy (ies), interval from delivery to first later conception	163.0	0	0.0
3. 1 plus 2	987.0	24	24.33
4. One later pregnancy; conception to follow-up observation	214.5	7	37.29
5. Two or more later pregnancies; interval from first to second conceptions	70.5	0	0.0
6. 4 plus 5	285.0	7	24.56
7. Two later pregnancies; interval from second conception to follow-up observation	96.0	1	10.41
8. Three or more later pregnancies; interval from second to third conceptions	21.0	0	0.0
9. 7 plus 8	117.0	1	8.55
10. Three later pregnancies; interval from third conception to follow-up observation	27.5	3	
11. Four or more later pregnancies; interval from third to fourth conceptions	5.5	0	
12. 10 plus 11	33.0	3	90.91
13. All cases with later pregnancy; interval from first later conception to follow-up observation	435.0	11	25.28

\*Mortalities reckoned from periods of follow-up after the later pregnancies, in an effort to determine the effect of the pregnancy.

TABLE III. REMOTE MORTALITY IN HYPERTENSIVE WOMEN, IN RELATION TO PREGNANCIES SUBSEQUENT TO THE ONE IN WHICH THE DIAGNOSIS OF HYPERTENSIVE DISEASE WAS ESTABLISHED\*

ATTAINED AGE	ALL PATIENTS						NO SUBSEQUENT PREGNANCY				ONE LATER PREGNANCY			TWO OR MORE LATER PREGNANCIES				
	EXPECTED ANNUAL DEATH RATE PER 1,000	PATIENT-YEARS EXPOSURE	ACTUAL DEATHS	EXPECTED DEATHS	RATIO OF ACTUAL TO EXPECTED DEATHS	ACTUAL ANNUAL DEATH RATE PER 1,000	ALL PATIENTS		OMITTING FIRST YEAR DEATHS		PATIENT-YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000	PATIENT-YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000		
							DEATHS	ANNUAL DEATH RATE PER 1,000	DEATHS	ANNUAL DEATH RATE PER 1,000								
20-29	2.460	276.5	6	0.28	8.8	21.70	116.0	4	34.48	115.0	3	26.08	76.0	1	84.5	1	11.83	
30-39	3.283	662.5	14	2.17	6.5	21.13	370.5	9	24.28	365.5	4	10.94	138.0	3	134.0	2	14.93	
40-49	5.384	453.0	14	2.42	5.8	30.90	309.5	10	32.29	308.5	9	29.18	101.0	3	42.5	1	23.52	
50-59	9.412	27.0	0	0.24	-	0.0	25.0	0	0.0	25.0	0	0.0	2.0	0	0.0	0	0.0	
Total	3.952	1419.0	34	5.6	6.1	23.96	821.0	23	28.02	814.0	16	19.66	337.0	7	261.0	4	15.32	
Standardized death rates																	20.90	16.77

\*Four immediate mortalities were omitted and the case of a 16-year-old girl who died two and one-half years after delivery.

The follow-up findings will be presented in relation to superimposed toxemia, and to subsequent pregnancies. There are 199 cases, since we have eliminated the 11 immediate and late puerperal deaths from this analysis; five patients refused examination, and three died without follow-up blood pressure recordings.

Table VI shows the distribution of blood pressures at follow-up. Of 125 patients who did not have superimposed toxemia, only 8.0 per cent had systolic pressures of 220 mm. Hg or higher. Of the 74 patients who did have superimposed toxemia, 24.3 per cent had systolic pressures of 220 or greater. Analysis by the Chi square method shows that the difference is significant—there are only two chances in 1,000 that the disparity is not real. This finding is to be considered in the light of the fact that the superimposition of pre-eclampsia or eclampsia is not related to the initial level of blood pressure as found before pregnancy or in the first trimester. In other words, the hypertension seems to be worse after toxemia.

TABLE VI. THE DISTRIBUTION OF BLOOD PRESSURES AT FOLLOW-UP, CORRELATED WITH PRESENCE OR ABSENCE OF SUPERIMPOSED TOXEMIA, AND WITH SUBSEQUENT PREGNANCIES

SYSTOLIC BLOOD PRESSURE AT FOLLOW-UP, MM. HG	LESS THAN 179		180 TO 219		MORE THAN 220		TOTAL
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES
No superimposed toxemia, total cases	79	63.2	36	28.8	10	8.0	125
No subsequent pregnancy	53	64.7	20	24.4	9	11.0	82
One subsequent pregnancy	11	52.4	9	42.8	1	4.8	21
Two or more subsequent pregnancies	15	68.2	7	31.8	0	0.0	22
Superimposed toxemia, total cases	31	41.8	26	35.2	17	23.0	74
No subsequent pregnancy	14	37.8	14	37.8	9	24.4	37
One subsequent pregnancy	11	42.3	9	34.6	6	23.1	26
Two or more subsequent pregnancies	6	54.5	3	27.3	2	18.2	11
Totals	110	55.3	62	31.2	27	13.5	199
No subsequent pregnancy	67	56.3	34	28.6	18	15.1	119
One subsequent pregnancy	22	46.8	18	38.3	7	14.9	47
Two or more subsequent pregnancies	21	63.6	10	30.3	2	6.1	33

This is more clearly shown by a comparison of the follow-up blood pressures with the levels initially observed. A follow-up blood pressure was not considered as higher than the original one unless the difference was more than 20 mm. Hg. In patients who did not have toxemia, 30.6 per cent had greater hypertension at follow-up, while in those who did have superimposed toxemia, 46.1 per cent had increased hypertension. There are only 3 chances in 100 that this is not a real difference.

The relation between toxemia and the incidence of increased hypertension at follow-up is more evident in the patients followed for shorter periods of time. In order to have enough patients in each category, we have divided them into two groups: those followed less than six years, and those followed more than six years. It will be seen from Table VII that in the group followed more than six years there is not a significant difference in the incidences of increased hypertension as between patients with and without superimposed toxemia. For the shorter periods of follow-up, the posttoxic patients do have a significantly higher incidence of aggravated hypertension. This is what might be expected if the toxemia contributes to the aggravation of the hypertension.

In our follow-up study of eclamptic and pre-eclamptic women we found, as had others, that the duration of the acute toxemia was very definitely correlated with the incidence of hypertension at follow-up. We have, therefore, sought for a relation between the duration of the superimposed toxemia and aggravation of the pre-existing hypertension. Our data are not ideal for this, because of the varying lengths of follow-up (many hypertensions become more severe with time). There were 55 cases for whom the duration of proteinuria

Since the highest death rate was found in the women with initial blood pressures of 200 mm. Hg or more, the question rises as to whether these patients escape later pregnancies, and contribute unduly to the mortality in our Group A (no subsequent pregnancy). Table V shows separately the relation between subsequent pregnancies, and the annual death rates for patients with initial blood pressures of less than and more than 200 mm. Hg. In those women whose initial pressures were 200 or higher, repeated pregnancies are associated with a somewhat lower death rate than is found in patients having no later pregnancy. However, the cases are too few to permit any definite conclusion. In the milder hypertensives, repeated pregnancy is associated with a slightly increased death rate. Two of the remote deaths occurred in later pregnancies (one being a rupture of the uterus), and might be considered as coming under the hazards of pregnancy itself. Without these deaths, the annual death rates would be slightly lower for women with pregnancies subsequent to the one in which the diagnosis of hypertensive disease was made.

TABLE V. THE RELATION BETWEEN REPEATED PREGNANCIES AND THE ANNUAL DEATH RATE IN WOMEN WITH MILDER AND MORE SEVERE INITIAL HYPERTENSION, RESPECTIVELY\*

INITIAL SYSTOLIC BLOOD PRESSURE, MM. HG	LESS THAN 200			MORE THAN 200		
	PATIENT- YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000	PATIENT- YEARS EXPOSURE	DEATHS	ANNUAL DEATH RATE PER 1,000
All cases	1272.0	23	18.08	150.0	12	80.00
No later pregnancy, all cases	717.5	14	19.52	106.5	10	93.90
No later pregnancy, excluding first year deaths	713.5	10	14.02	103.5	7	67.62
Later pregnancy, all patients	554.5	9	16.22	43.5	2	45.97
Later pregnancy, ex- cluding two deaths in pregnancy	552.5	7	12.66	43.5	2	45.97

\*Four immediate maternal mortalities were omitted.

Another factor of selection lies in the relative numbers of patients who have pregnancies following hypertensive pregnancies with and without superimposed toxemia, since posttoxemic women fare much worse than those who escape toxemia. Of the 82 women who had superimposed toxemia, 23, or 28.1 per cent, had later pregnancies. Of the 136 patients who escaped toxemia, 59 or 43 per cent, had later pregnancies. Thus our Group A (no subsequent pregnancy) is slightly weighted with posttoxemic patients who do poorly, and Groups B and C contain a selection of favorable cases. However, a separate analysis of patients with and without superimposed toxemia shows no significant differences in annual death rates for those who did and those who did not have pregnancies after the one in which the hypertensive disease was diagnosed.

In summary, during the period of follow-up (average seven years), *repeated pregnancies in these hypertensive women have not significantly increased the annual death rate.*

### Severity of Hypertension at Follow-Up

Not all patients had hypertensive levels of blood pressure when re-examined. Twenty-six, or 11.9 per cent, had either a systolic pressure of less than 140 mm. Hg, or a diastolic pressure of less than 90 mm. Hg, or both. Of the 23 diastolic pressures below 90, 18 were in the 80's, and of the 17 systolic pressures below 140, 11 were in the 130's. Only two patients had pressures of less than 130/80 in both systolic and diastolic readings.

"trace" of protein (possibly significant), and 16 had 1 Gm. or more per liter. Of the 16 urines with significant degrees of proteinuria, 10 were terminal findings, and four others were those of patients in some degree of cardiac decompensation.

### Renal Function at Follow-Up

In 72, or 37.1 per cent, the urinary specific gravity was 1.022 or higher in casual urines. This we take to mean normal renal function<sup>3</sup>; the urea clearances done in 45 of these cases were all in the normal range. Urea clearances were done in 81 of the 122 patients whose urinary specific gravity readings were less than 1.022. There were only 14 clearances below 70 per cent, and eight of these were between 60 and 69 per cent.

Of the patients whose renal function was estimated, 96 per cent were normal. Four additional patients died of renal failure, and 21 others died without renal functional evaluation.

Five of the six patients with clearances below 60 per cent had had superimposed pre-eclampsia.

TABLE VII. AGGRAVATED HYPERTENSION AT FOLLOW-UP (AS COMPARED WITH INITIAL HYPERTENSION), IN RELATION TO LENGTH OF FOLLOW-UP

	LENGTH OF FOLLOW-UP			
	LESS THAN SIX YEARS		MORE THAN SIX YEARS	
	CASES	INCREASED HYPERTENSION PER CENT	CASES	INCREASED HYPERTENSION PER CENT
No superimposed toxemia	64	20.3	61	41.0
Superimposed toxemia	33	39.4	41	53.7
p (chances in 100 that difference is not significant)		5.0		21.1

TABLE VIII. THE BLOOD PRESSURE AT FOLLOW-UP IN COMPARISON WITH THE INITIALLY OBSERVED LEVEL CORRELATED WITH THE PRESENCE OR ABSENCE OF SUPERIMPOSED TOXEMIA, AND WITH SUBSEQUENT PREGNANCIES

BLOOD PRESSURE AT FOLLOW-UP	LOWER		SAME $\pm 20$ MM.		HIGHER		TOTAL CASES
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	
No superimposed toxemia, total cases	25	20.0	62	49.6	38	30.4	125
No subsequent pregnancy	15	18.3	41	50.0	26	31.7	82
One subsequent pregnancy	2	9.5	11	52.4	8	38.1	21
Two or more subsequent pregnancies	8	36.4	10	45.5	4	18.2	22
Superimposed toxemia, total cases	16	21.6	23	31.1	35	47.3	74
No subsequent pregnancy	9	24.3	11	29.7	17	46.0	37
One subsequent pregnancy	4	15.4	8	30.8	14	53.8	26
Two or more subsequent pregnancies	3	27.4	4	36.3	4	36.3	11
All patients	41	20.6	85	42.7	73	36.7	199
No subsequent pregnancy	24	20.2	52	43.7	43	36.1	119
One subsequent pregnancy	6	12.8	19	40.4	22	46.8	47
Two or more subsequent pregnancies	11	33.3	14	42.4	8	24.3	33

### Subsequent Pregnancies

There were 127 pregnancies in 82 patients, subsequent to the one in which the diagnosis of hypertensive disease was made. The fetal loss in these later pregnancies was 51, or 40.2 per cent. Of these later pregnancies, 83 were delivered (or aborted) in this hospital, and are included in our analysis. The other 44 were either delivered or aborted at home or in other hospitals.



is known. Twenty-seven were carried for less than three weeks with proteinuria; 11, or 40.8 per cent, now have a greater hypertension than they had initially. In 28 cases, the proteinuria existed for more than three weeks; 17, or 60.7 per cent, now have an aggravated hypertension. The difference is not striking, since there are 13.5 chances in 100 that it may not be significant. The total maternal mortalities in the two groups are 18.5 and 25 per cent, respectively.

The initial level of blood pressure seems to have some bearing upon the incidence of increased hypertension following superimposed toxemia. As perhaps might be expected, a larger proportion (68 per cent) of mild hypertensives become worse (as judged by the blood pressure level). When the patients began with a severe hypertension, only 31 per cent became worse. This is shown in Fig. 1, which depicts the proportions of patients with aggravated diastolic hypertension. In those patients who escaped superimposed toxemia, the initial level of the diastolic pressure does not bear a significant relation to the incidence of increased hypertension as found at follow-up.

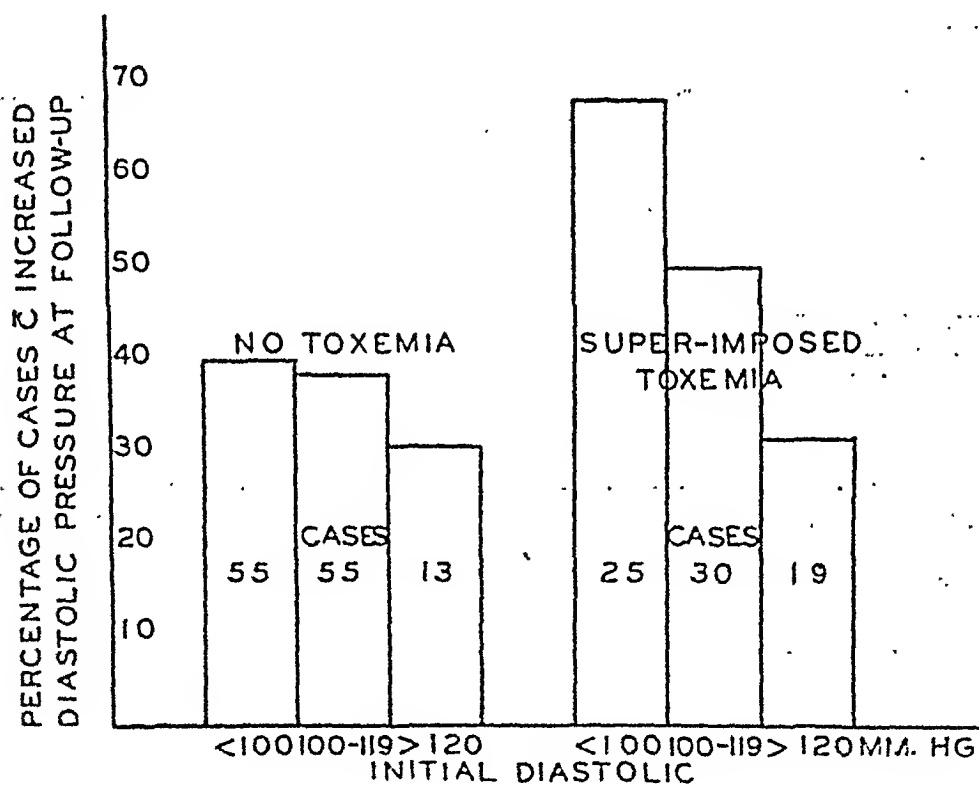


FIG. 1.

There was no relation between the patients' ages and the severity of hypertension at the time of re-examination.

It appears that repeated pregnancies do not result in an increased incidence of either severe hypertension or in aggravation of the hypertensions, even with the risk of superimposed toxemia (Tables VI and VIII). In fact, just as in the death rates, the patients having two or more subsequent pregnancies are, on the average, somewhat better off than those having one or no later pregnancy.

#### Proteinuria at Follow-Up

The voided urines of 194 patients were examined at follow-up. In 83.6 per cent, protein was either negative or present in only a "very faint trace," which is a normal finding by the sulfosalicylic acid method. Sixteen urines showed a

serious course in the younger patients. If the toxemia *causes* the damage, then the prompt interruption of a hypertensive pregnancy at the first sign of developing toxemia should benefit the patient. Moreover, the courageous adherence to this policy would allow us to give any hypertensive a "trial of pregnancy." On the other hand, if the appearance of toxemia points to a vascular system which cannot withstand the hypertensive disease, then the prognosis is bad, regardless of pregnancy.

The midpregnancy drop in blood pressure has a very practical importance for diagnosis. An appreciable number of our hypertensives had perfectly normal blood pressures over several weeks of the second and third trimesters. Had their earlier hypertensive pressures been unknown, and had they first been seen in midpregnancy—as so many patients are—they would have been classified as pre-eclampsia. This factor also confuses the interpretation of permanent hypertension apparently left as a sequel of "pre-eclampsia."

### Summary and Conclusions

From the opening of the hospital in October, 1931, through 1944, we have seen 218 patients in 301 pregnancies classifiable (from recorded blood pressures) as hypertensive toxemia.

Every patient was traced to late 1945 or early 1946. Of the 218, 39 are dead, 5 refused examination, and 178 were re-examined (four have died since re-examination).

The gross fetal loss:

In earlier pregnancies, 35 per cent

In the first hypertensive pregnancy, 38 per cent

In subsequent pregnancies, 40 per cent

Nearly 40 per cent of the hypertensive patients showed drops in blood pressure in midpregnancy.

Proteinuria occurred in half of the pregnancies.

Renal function tests were normal:

During pregnancy in 93 per cent

At follow-up in 96 per cent

The fetal mortality is increased by:

Higher initial blood pressures

Blood pressure rises in the second trimester

Higher pressures near delivery

Decreased renal function

Proteinuria

Superimposed toxemia

There were six immediate maternal deaths:

Four in first hypertensive pregnancy

Two in subsequent pregnancies

There were seven late puerperal deaths, making a total maternal mortality of 4.3 per cent, or 20 times the general rate for the same period.

In the pregnancies which we saw, the recurrence rate of superimposed toxemia was 64 per cent. In pregnancies following nontoxic gestations, the incidence of superimposed toxemia was 25.4 per cent.

### Discussion

Our analysis has confirmed what others have found about the immediate hazards of pregnancy, both to the hypertensive mother and to her fetus. The incidences of pre-eclampsia, eclampsia, maternal and fetal death are increased several fold. In our series, the maternal mortality in 301 hypertensive pregnancies was 4.3 per cent, including seven late puerperal deaths, some of which occurred elsewhere. This is 20 times the general rate in our clinic. Four of the late puerperal deaths were uremic, and it is quite possible that pregnancy may have accelerated the renal decompensation. However, one of these deaths occurred six weeks after a therapeutic abortion which was done at sixteen weeks. In another case, there was some evidence of the onset of malignant hypertension before conception. The other two patients were not seen until late in pregnancy, at which time their urea clearances were less than 30 per cent. The times of onset of the malignant phase of hypertension are unknown, although both had had severe hypertension two and three years, respectively, before conception.

Our follow-up study has not confirmed the supposition that pregnancy is remotely harmful to the hypertensive patient. Individual cases may suffer acceleration of the disease should they develop superimposed toxemia, but these cases are all but lost in the averages.

In order to assess the remote effects of pregnancy upon the hypertensive disease, we have compared three groups of patients: those with no pregnancy subsequent to the one in which the diagnosis of hypertensive disease was made, those with one later pregnancy, and those with two or more later pregnancies. Thus all women had at least one hypertensive pregnancy. The ideal control series would be nulliparous women, or women who have had therapeutic abortions done for the hypertensive disease. Lacking such a series, we have had to resort to the method used.

Our bases for comparison of the three groups have been: mortality, annual death rates, severity of hypertension at follow-up, proportions with follow-up blood pressures higher than the initially observed levels, and the renal, cardiac, and eyeground status. In the averages, repeated pregnancies are without demonstrable effect by any of these criteria.

As has already been pointed out, the major hazard of pregnancy in the hypertensive woman is the superimposition of toxemia. In addition to the increased maternal and fetal mortality which this complication carries, it also leaves some patients with severe and aggravated hypertension.

We cannot say that the pre-eclampsia caused the aggravation of the hypertension, for it is possible that the vascular system susceptible to toxemia is also more susceptible to the ravages of the hypertensive disease itself. Perhaps it is significant in this connection, that superimposed toxemia is more common in the younger hypertensives; it is well known that hypertension follows a more

# PLACENTAL METABOLISM OF VITAMIN C

## II. Histochemical Analysis

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IN THE course of studying the placental metabolism of ascorbic acid, it becomes necessary to determine the localization of the vitamin within the tissues. The findings of Javert and Stander,<sup>1</sup> as well as of King,<sup>2</sup> imply an etiologic relationship between ascorbic acid levels and spontaneous abortion. Such a mechanism would presumably depend, however, more on the vitamin concentrations and (possibly) localization in the tissues involved, than simply on the levels discovered in the maternal plasma. Gross analyses have revealed no constant factor relating the maternal blood levels with placental concentrations of ascorbic acid<sup>3</sup> and the present paper presents the corollary histochemical determinations.

Histochemical studies of the iron, glycogen, lipoids, phosphatase, and calcium content of the human placenta have been reported by Dempsey and Wislocki,<sup>4, 5</sup> and Gellhorn<sup>6</sup> has recently demonstrated the cystologic aspects of sodium metabolism, using the radioactive ion. Ascorbic acid itself has been localized and studied in the adrenal, hypophysis, and ovary,<sup>7-9</sup> Giroud and Leblond<sup>8</sup> even demonstrating that the fixation of the vitamin in the corpus luteum undergoes a cyclic change as the lutein cells do. On approaching the problem in placental tissue, however, it proved necessary not only to establish the normal in the term placenta, but also to review critically the techniques available for ascorbic acid localization.

The reducing action of ascorbic acid on silver nitrate has provided the basis for most of the methods advanced for staining the vitamin. The difficulties attendant upon applying such a procedure to placental tissue fell into three groups: (a) the solubility of vitamin C in the various reagents used, (b) the degree of tissue penetration attained by the silver nitrate solution, and (c) the presence of other reducing substances in the placenta which might give false reactions. In the course of evaluating these difficulties and establishing a stain technique, over 500 placentas have been examined by one of us (J. H. H.).

### Technique

1. A 2 to 3 millimeter slice of fresh placental tissue is cut by frozen section.
2. The tissue is floated onto 5.4 per cent levulose for ten minutes.
3. The tissue is placed in acidified silver nitrate solution and kept in the dark in an incubator at 56° C. for twenty minutes.
4. The impregnated tissue is washed in distilled water for fifteen to twenty minutes to remove the excess silver salts.
5. The silver stain is fixed in 5 per cent sodium thiosulfate for thirty minutes.

The annual death rate of the 214 survivors was 24.62 per thousand, which is six times the expected rate for unselected women of the same age, color, and calendar year distribution.

In the 82 patients who had superimposed toxemia, the annual death rate was 43.25 per thousand, in contrast to 14.24 in patients who escaped toxemia.

*Repeated pregnancies, even with the risk of toxemia, did not increase the death rate.*

The superimposition of toxemia is followed by an increased incidence of severe and of aggravated hypertension.

Repeated pregnancies did not increase the incidence of severe, or of aggravated hypertension, despite the risk of toxemia.

The outstanding conclusion is that repeated pregnancies are not demonstrably harmful to the hypertensive woman. The pregnancy itself is hazardous should toxemia occur. Such superimposition of toxemia also does harm some individual patients.

We wish to express our gratitude to Dr. S. A. Cosgrove, Dr. J. F. Norton, and Dr. E. G. Waters for reading the typescript. Dr. Harry Perlberg read the chest plates, for which we are indebted to the x-ray department. Many physicians have given us permission to re-examine their private patients, and several doctors—as far afield as South Carolina—have examined patients for us. Mrs. E. H. Rafton, and especially Mr. M. Spiegelman of the Metropolitan Life Insurance Company have given us valuable help with the mortality tables. The superintendents and Record Room personnel of every hospital in Hudson County have cooperated in helping us to trace patients. Most of the urea clearances and blood chemistries were done by Misses Doris Furze and Eleanor Brudnicki, who also helped in checking hospital records.

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6. The tissue then is placed in absolute alcohol for twenty-four hours previous to embedding in paraffin and staining with hematoxylin-eosin.

*Discussion of Technique.*—Prior to establishing the above routine, every reagent or procedure used or feasible was tested for its tendency to dissolve vitamin C out of the tissues. One gram pieces of tissue were frozen on the frozen-section block, thawed, and assayed for ascorbic acid content. The mean loss was 6 per cent  $\pm 2$ , and, although the tissue so cut is exceedingly difficult to handle, this provided our best method of sectioning which assists in the penetration of the stain. Methyl, ethyl, and butyl alcohols were all checked as possible fixative agents, but were found to remove too much ascorbic acid from the tissues. It has been demonstrated by Bourne<sup>10</sup> that formalin vapor interferes with the silver stain and does not make a satisfactory method of fixation.

Step 2 is necessary to remove excess chlorides, and the problem was presented of finding a washing solution which would neither remove the vitamin nor distort the cells. While 10 per cent levulose produced the smallest loss of vitamin C, its hypertonicity resulted in cell damage, and 5.4 per cent levulose (approximately isotonic) was used. With isotonic levulose there is loss of C from the tissues of less than 10 per cent in the period of time that the washing continues.

The silver nitrate solution of step 3 is a 5 per cent solution to which is added 0.5 c.c. glacial acetic per 100 c.c. The addition of the latter increases the specificity of the reaction, ascorbic acid being the principal substance which gives the argentaffin reaction in an acid medium. The 10 per cent silver nitrate recommended by Giroud and Leblond<sup>8</sup> was found to give too much tissue distortion. A 5 per cent solution provides maximum impregnation with minimum cell distortion.

The incubation involved in the third step presented a problem. Admittedly at this temperature the oxidation of the vitamin will be more rapid. However, the procedure was found to increase penetration of the tissue by the silver nitrate, and for this purpose was of great value. It must be remembered, furthermore, that while the vitamin is heat labile, the vitamin-silver nitrate complex is not, so that as soon as the stain penetrates the microscopic section to reach the ascorbic acid, loss of the latter through elevation of the surrounding temperature ceases. After comparative studies it was felt that there was no appreciable loss from the twenty minutes of 56° C. and the penetration of  $\text{AgNO}_3$  into the tissue was definitely increased.

Similarly, the vitamin-silver nitrate complex is not (in contrast to the vitamin itself) water soluble, so that the washing in step 4 can be carried out in distilled water without danger of loss of substance. Such washing must be carried out in the dark, however, since the silver salts have not yet been fixed. Absolute alcohol was selected as the tissue fixative (Step 6) because formalin causes the precipitation of a dense black artifact in the presence of any excess silver salt.

To evaluate the amount of reduction of the silver nitrate resulting from other substances, the technique was applied to prepared gelatin blocks. Four sections were used: plain gelatin, gelatin with glucose, gelatin containing glucuronic acid, and gelatin containing ascorbic acid. The amount and intensity of the color developed by the ascorbic acid are quite distinct from that formed by the weaker reducing agents, and it is doubtful that there is a significant amount of stain in the final sections which represents reduction of the silver salt by nonvitamin substances.

*Results.*—The photomicrographs in Figs. 1 and 2 indicate the typical distribution of the vitamin in placental tissue. From these it can be seen that the heaviest concentration of the ascorbic acid lies at the syncytial layer of the villi.

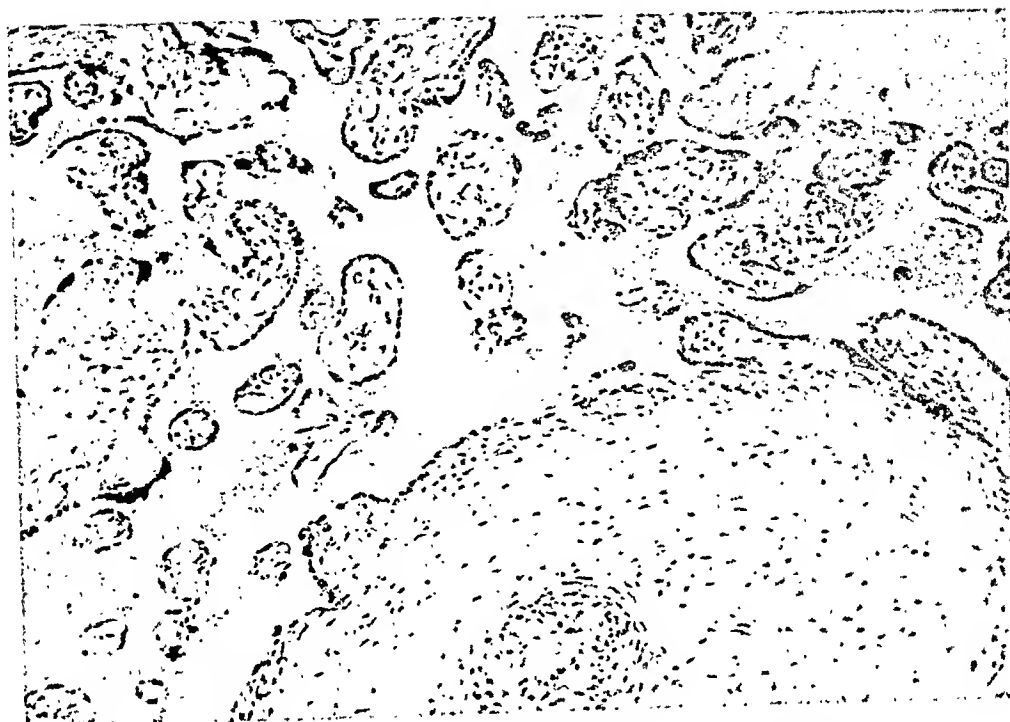


Fig. 1.—Section of placenta stained with hematoxylin-eosin without treatment with silver nitrate.

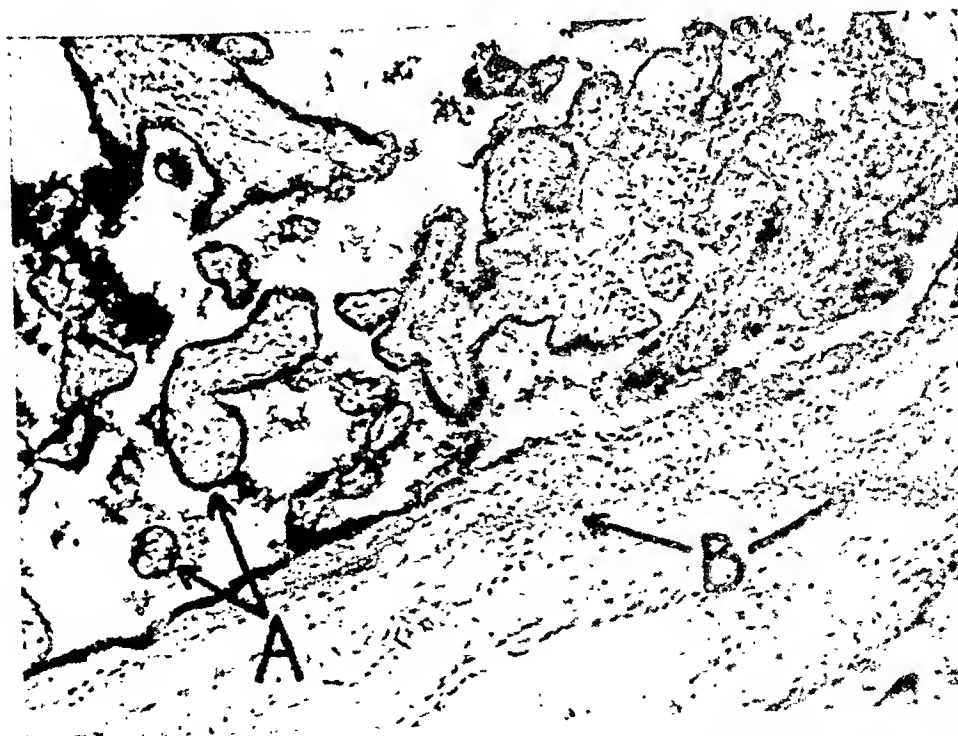


Fig. 2.—Silver nitrate stain, adjacent section of placenta. (A), Heavy deposition of ascorbic acid in syncytial layers. (B), Fine granules of stained ascorbic acid in stroma.

human placenta reveals that the greatest concentration of ascorbic acid lies at the syncytial layer of the villus. A smaller portion was demonstrated within the stroma of the villus, but there is consistently more of the vitamin in the fetal than in the maternal portion of the placenta.

The histochemical studies here reported were carried out by Dr. Holzaepfel in partial fulfillment of the requirements for the degree of Master of Medical Science.

The authors wish to express their appreciation to Mrs. Rosalie York and Miss Eloise White for their technical assistance.

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There is some C in the central core of the mesodermal connective tissue, as evidenced by an even distribution of granules. The granules in this area, however, are not as heavily deposited as at the syncytial layer. While the technique employed permits of quantitative conclusions only in the face of marked differences in staining, it was noted in all slides that the fetal portion of the placenta is richer in the vitamin than is the maternal portion.

### Discussion

The distribution revealed in these studies is a reflection of the gradient of physiologic activity in the villus. Most of the metabolic function occurs at the syncytial layer, the area of maternal-fetal interchange, and in term placentas the principal evidences of degeneration and cytolysis lie in the center of the villi.

Bourne<sup>7</sup> has stated that there is a perinuclear aggregation and an outlining of the Golgi apparatus and mitochondria by deposition of ascorbic acid granules. While this statement may or may not be true with respect to the adrenal, on the basis of the work here reported, it can be unequivocally denied with respect to the placenta. No perinuclear aggregation or definite intracellular localization is noted in any of the placental tissues examined, and it would seem remarkable if a substance as highly soluble as is ascorbic acid should follow a definite pattern of localization inside a cell. Furthermore, statements as to intracellular localization must be accepted with reservation until it can be demonstrated that the granules of silver nitrate do not migrate after precipitation. While such migration may occur intracellularly,<sup>11</sup> intercellular migration is doubtful, and the conclusions reached above as to the localization of the granules in various tissue areas undoubtedly represent the true distribution of the vitamin.

It is of interest to compare these findings with other reported localizations within placental tissue. Ribonucleoprotein and alkaline phosphatase are both also found predominantly in the syncytial layer. Their relationship is an inverse one, however, the ribonucleoprotein being high in early pregnancy and decreasing as the alkaline phosphatase rises.<sup>4</sup> We have, in the course of this work, interrupted the pregnancies of rabbits at thirty and at sixty days for stains of the ascorbic acid in the placental tissue, and we can see no differences in concentration which can be related to the duration of the pregnancy.

Dempsey and Wislocki<sup>4, 5</sup> have also postulated that the syncytium is the site of the production of placental steroids on the basis of histochemical evidence. They have observed in this layer a positive Schiff's reaction and a greenish fluorescence (both of which are abolished by preliminary treatment of the tissues with alcohol or acetone) as well as stainable fat droplets which are birefringent. Glycogen is not laid down primarily in the syncytial areas, being found principally where vascularization is poor and the oxygen tension low. Iron is distributed in both syncytium and stroma, not showing the sharp gradient which we have observed with ascorbic acid.

### Summary and Conclusions

A modification of the silver nitrate method for the microscopic localization of vitamin C in tissues is presented. Application of this technique to the

The onset of the illness was acute and was somewhat similar to food poisoning, and indeed this was the tentative diagnosis at the time of admission. She had begun menstruating at the age of 13 years, her periods were regular at intervals of twenty-eight days, the duration of flow was eight to ten days and the flow was rather profuse, requiring about 24 napkins during the entire period. There was only a moderate amount of cramplike pain during the first two days of the flow. Her last menstrual period had stopped about ten days before the onset of the present illness. General examination was negative, save for marked tenderness and some rigidity in both lower quadrants of the abdomen. Temperature on admission was normal, and the white blood cell count was 7,800 with a normal differential. The following day her temperature rose to 102° F., she continued to have vomiting and diarrhea, complained bitterly of cramplike pain in the lower abdomen and backache, and developed a rather profuse white vaginal discharge. The abdomen became rather markedly distended and tender, and it appeared as though there was a mass on either side of the midline just above the symphysis. Pelvic examination confirmed the presence of the masses, but there was such marked tenderness in the pelvis that a satisfactory examination could not be done. There was a rather abundant amount of white milky discharge exuding from the cervix. Repeated smears of this discharge showed only pus with very few organisms and no gram-negative diplococci.

The pain, backache, vomiting, and diarrhea persisted, and the abdominal distention became more marked. The stomach was kept emptied by means of continuous suction through a duodenal tube. It was obvious at this time that the patient had a pelvic peritonitis and there was a peculiar "doughy" sensation present upon palpating the abdomen. The possibility of a tuberculous peritonitis was considered, and during the fourth and fifth days of her illness this seemed the most likely diagnosis. She ran daily temperatures to 100° to 101° F., the white count remained within the normal range, the highest point reached was 9,200 on the seventh day of the illness, the pain and diarrhea persisted, and then on the eighth day of her illness she became suddenly better, her temperature gradually returned to normal and remained there. She was discharged from the hospital on the nineteenth day. She was afebrile during the last eleven days.

Following discharge from the hospital the patient returned rapidly to her normal health. The rapid recovery disproved our diagnosis of tuberculous peritonitis. It was doubtless that she had had a pelvic peritonitis, but the etiology was far from clear. It was not until about six weeks after her illness that a plausible cause was found. During the course of a pelvic examination, a small slitlike opening was seen on the left side of the vagina just inside the hymeneal ring. Exploration of this opening revealed another vagina, smaller than the one on the right, and further exploration revealed another cervix which was connected to the mass on the left side. Upon finding this anomaly in the pelvis, the theory was postulated that the patient had had a temporary blockage of the left side with retrograde menstruation into the peritoneal cavity. This opinion was substantiated to some degree at a later date when the patient had a cesarean section. The left tube was found to be patent with a delicate fimbriated end, but there were many weblike adhesions between the tube and broad ligament.

The patient was then seen in August, 1939, eight months after her illness, because of a period of amenorrhea of two months' duration. Her last menstrual period was June 7, 1939, and her expected date of confinement was March 14, 1940. On examination the right uterus was enlarged to about the size of an eight to ten weeks' pregnancy and was soft. The left uterus was slightly enlarged and was well out of the pelvis. Her antepartum course was not re-

## PREGNANCY AND THE DOUBLE UTERUS

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**A**NOMALIES of the female reproductive system, manifested by various degrees of failure of fusion of the Müllerian ducts, are not uncommon, and many reports have been made in the recent literature. This paper is concerned only with the true double uterus with double cervix, an anomaly which is not seen frequently, and because the patient here reported has been observed during the courses of four pregnancies, it was thought worth while to report her case somewhat in detail. Of additional interest is the fact that she was seen during the course of a rather unusual illness prior to her first pregnancy.

It is important to have a clear understanding of what we mean by the term double uterus. Some writers include bicornate uterus and septate uterus in this general term. Taylor<sup>1</sup> makes a plea for a simple classification and suggests the following:

1. Uterus arcuatus
2. Double uterus with single cervix
3. Septate uterus with a single or a septate vagina
4. Double uterus with a double cervix
5. Uterus with a rudimentary horn or absence of one horn

This classification is far more simple than most offered, but still does not give as clear an anatomic picture as that of Way.<sup>2</sup> Way's classification is self-explanatory and obviates the possibility of any confusion.

1. Uterus arcuatus with a notch in the top of the fundus which does not extend through the entire thickness of the myometrium, and thus does not alter the conformity of the uterine cavity.
2. Uterus bicornis, unicorpus, unicollis, which as the name connotes means two cornua, one body, and one cervix.
3. Uterus bicornis, unicollis. Two bodies and one cervix.
4. Uterus bicornis, bicollis. Two bodies and two cervices.
5. Uterus sub-septus. One uterus which has an incomplete septum.
6. Uterus septus. One uterus with a complete septum which divides the uterine cavity and cervix in two halves.

Anomalies of the uterus may arise in one of three ways: (1) failure of fusion of the Müllerian ducts, (2) persistence of the median walls, and (3) through failure of development. Although the normal uterus is a midline organ, it is bilateral in origin and has a bilateral nerve and blood supply. Rudolph<sup>3</sup> states that in the uterus simplex the fused medial walls of the Müllerian ducts are resorbed in a caudo-cranial direction. Arrest in the resorption of the fused medial walls at different levels gives rise to various types of anomalies. Failure of fusion of the Müllerian ducts is responsible for the true double uterus with double cervix. It is this particular type of deformity with which this paper is concerned.

### Case Report

This patient was first seen Dec. 3, 1938. At that time she was 23 years old and had been married two months. She was admitted to the hospital because of severe lower abdominal pain, backache, nausea and vomiting, and diarrhea.

and began bleeding profusely. During the course of about an hour she passed approximately 600 c.c. of blood. Following the bleeding her membranes ruptured. The patient was given a transfusion of 500 c.c. of whole blood and, without anesthesia, a sterile vaginal examination was carried out. This examination revealed the fact that the right uterus was incarcerated in the hollow of the sacrum, down in front of the infant's head. The cervix of the pregnant uterus was long, dilated sufficiently to admit one finger, and placental tissue was felt over the internal os. In view of these findings, the decision was made to deliver the patient by section. Under local anesthesia, low-flap cesarean section was performed, and a normal premature male weighing 4 pounds, 6 ounces was delivered. The placenta was implanted on the lower uterine segment and partially covered the internal os. Inspection of the pelvis was interesting. There were two completely separate uteri with the pregnancy in the left uterus. The right uterus was slightly enlarged and was completely retroverted and lying in the hollow of the sacrum down in front of the presenting part of the infant. There was one normal tube and ovary on each uterus, on their lateral aspect. The left tube was adherent to the posterior leaf of the left broad ligament by several filmy weblike adhesions. The fimbriated end was delicate and patulous. There was a rudimentary round ligament on the medial aspect of the right uterus.

The patient had a very stormy convalescence complicated by atelectasis, bronchopneumonia, and a low grade peritonitis. The abdominal symptoms and findings were very similar to her first illness. She had severe abdominal cramps, diarrhea, vomiting, and the same "doughy" distention which characterized her first illness. Involution of both uteri was slow and there was never any evidence of passage of a decidual cast. She was finally discharged from the hospital on March 10, 1946. The baby did well, and upon discharge on April 12, 1946, weighed 9 pounds, 9 ounces.

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markable, except for slight vaginal bleeding on one occasion at about ten weeks. On Dec. 30, 1939, when she was about twenty-six weeks pregnant, the left uterus was found to be partially in the true pelvis and exquisitely tender. On Feb. 27, 1940, two weeks before term, the head was dipping well into the pelvis, and the left uterus was entirely out of the pelvis. The patient went into labor spontaneously on March 11, 1940, and after an uneventful labor of eight hours delivered spontaneously a normal term female weighing 5 pounds, 14 ounces. There was no laceration of the perineum, but the septum was torn from its attachment to the anterior wall of the vagina. The placenta separated immediately and was expressed intact. There was no appreciable blood loss. The patient had an afebrile uncomplicated puerperium, and was discharged from the hospital on the fourteenth postpartum day.

*Second Pregnancy.*—On Dec. 9, 1940, nine months after her first delivery, the patient returned for care of her second pregnancy. Her last menstrual period was Sept. 7, 1940, and her expected date of confinement was June 14, 1941. On this examination the *left* uterus was found to be enlarged to about the size of a ten to twelve weeks' pregnancy. The right was also slightly enlarged but firm. Her antepartum course was normal and on April 26, 1941, approximately six weeks before term, the fetal head was well engaged in the pelvis and the right uterus was out of the pelvis. The patient then went into labor prematurely four weeks before term and, after an uneventful labor of six hours, delivered spontaneously a normal premature female weighing 4 pounds, 13 ounces. The placenta separated immediately and there was no appreciable bleeding during the third stage. Her puerperium was again afebrile.

*Third Pregnancy.*—The third pregnancy occurred while the author was in the service and no personal observation was made. In April, 1943, during her tenth week of pregnancy, the patient began to have vaginal bleeding which persisted for five days. On the fifth day she developed cramps on the right side and expelled a fetus with the placenta. Twenty-four hours later she developed cramps on the left side of her abdomen and expelled another fetus intact with the placenta. It was the impression of the physician who attended her that she was pregnant in both uteri.

*Fourth Pregnancy.*—The patient was first seen on Oct. 2, 1945, in the fourteenth week of her fourth pregnancy. The last period was on June 14, 1945, and the expected date of confinement was March 21, 1946. She gave a history of having passed about one-half cupful of clear fluid during the tenth week of her pregnancy, and had remained in bed for about a week because of lower abdominal cramps and the passage of fluid. On examination she was found to be pregnant in the left uterus, and the enlargement of the uterus corresponded with the period of amenorrhea. Her prenatal course was again essentially normal, with the exception of the fact that she had rather constant aching pains in the lower abdomen, particularly on the right.

At 4:30 A.M. on Jan. 25, 1946, in the thirty-second week of her pregnancy, she was suddenly awakened by a gush of blood estimated to be 50 to 60 cubic centimeters. A few minutes later she developed abdominal cramps and backache and passed what she thought was amniotic fluid. She was admitted to the hospital and given morphine in an attempt to prevent premature labor. A compatible donor was obtained and no rectal or vaginal examination was done. For the next ten days the patient continued to bleed moderately at intervals, particularly at night, and associated with the bleeding was regular and painful uterine contractions. She was given daily injections of estrogen and progesterone in an attempt to prevent premature labor, and on numerous occasions it was necessary to administer narcotics. The fetus was presenting by vertex and the head was floating above the pelvic brim. Finally, on the morning of February 3, approximately seven weeks from term, she developed hard labor pains

dilated, and a small but continuous flow of blood appeared at the vulva. After twenty-two and one-half hours' labor, rectal examination revealed a fleshy mass in front of the head. The head had descended to well below the spines. At vaginal examination the mass was recognized as a detached annular portion of the cervix. The annular detachment was complete except for a 2.5 cm. tag of tissue at about 11 o'clock. After twenty-three hours of labor under ethylene anesthesia, the patient was delivered of a normal 3,300 Gm. female infant by low forceps in left occiput anterior position. The tag of cervix described above was clamped, cut, and tied.

There had been a moderate amount of vaginal bleeding during the last eight hours of the first stage. 750 c.c. of blood loss was collected in the delivery room. The estimate prior to delivery was 350 c.c., making a total of 1,100 c.c. blood loss during labor. The placenta separated spontaneously after 7 minutes of the third stage, and was expressed by modified Credè. The bleeding during the first stage probably came from the cervical lesion, with a small amount from the cervix during the second stage. The greater amount was from the uterus during the third stage.

Nineteen days post partum, a small rim of vaginal cervical tissue was present. On the patient's left, a tag remained about 4 millimeters in length. The artificial os admitted the tip of a finger.

Fourteen weeks post partum, the external os was rigid and very small. The patient had experienced three normal menstrual periods. She complained of an acquired dysmenorrhea that had increased since delivery.

Twenty months after delivery, the patient had avoided a repeat pregnancy. Her acquired dysmenorrhea was much less severe. The pelvic examination was essentially the same at this visit as when seen 14 weeks post partum.

*Pathologist's Report.*—The specimen consisted of a roughly hemispherical ring of dark bluish-red, rather friable tissue, measuring 5.5 cm. in diameter, with an opening 3 cm. wide. The tissue varied in thickness, with an average of 2 cm. Cut surfaces were solid, dark red, and friable after formalin fixation.

Sections cut parallel to the cervical canal showed a convex border covered by stratified squamous epithelium with transition to columnar cells and tubular glands at about the midpoint. The whole epithelial layer was stretched thin, and there was an infiltration of polymorphonuclear leucocytes and fibrin between the cells and on the surface. The lamina propria was fibrillary, markedly edematous, and sparsely infiltrated with leucocytes. The deeper structure was fibrous, with widely separated fibers with edema and extensive fresh hemorrhage between them. There were many distended, thin-walled blood vessels present, and the deep border of the tissue was made up of a fairly uniform layer of connective tissue strands and smooth muscle fibers, some lying parallel to the line of separation, while others appeared to have been disrupted tangentially or at right angles.

*Pathologic Diagnosis.*—Acute congestion, hemorrhage, and edema of cervix uteri, with spontaneous amputation of the pars vaginalis.

In this case, the cause given for cesarean section was "poor dilatation of the cervix." During the patient's second labor no apparent disproportion existed. The cervix was slow in dilating, and was definitely rigid. It tore away when the pains became hard following spontaneous rupture of the membranes.

One might believe that the starting point of separation would show an area where prolonged pinching had produced ischemia and necrosis. The detached specimen showed no area of necrosis along its peripheral edge, either grossly or histologically.

## SPONTANEOUS ANNULAR DETACHMENT OF THE CERVIX DURING LABOR

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**A**NNULAR detachment of the uterine cervix occurring during labor is a rare complication. In 1933, DeCosta<sup>1</sup> collected reports of seventeen instances of this complication, including one of his own. In a thorough search of the literature, we have been able to find but fifty-four reported cases, and are reporting an additional instance which came under our observation.

The first recorded instance of this complication of labor was by Scott<sup>2</sup> in 1821. Including our own, there are but seven such cases occurring in the American literature, the first by Johnston<sup>3</sup> in 1851.

We have omitted one case reported as occurring in a two months' abortion and one other complicated by carcinoma of the cervix occurring during labor which appears in Meigs'<sup>4</sup> textbook on obstetrics, published in 1856, as not being representative of spontaneous amputation occurring during labor.

### Case Report

Mrs. H. J. S., aged 22 years, white, para i, gravida ii, was first seen prenatally on Sept. 11, 1944. At this time she was one month from term.

Her past obstetric history revealed that on Feb. 9, 1942, she had been delivered elsewhere by cesarean section. The indications given were "a difficult, prolonged labor, poor progress, a head in transverse arrest, and failure of the cervix to dilate satisfactorily after thirty-six hours of labor." The postoperative course was uneventful. The infant born in 1942 weighed 3825 grams.

The prenatal course of the pregnancy here reported was normal. The pelvic measurements were as follows:

I.S.—26 cm.

I.C.—29 cm.

I.T.—32.75 cm.

B.D.—21 cm.

D.C.—12.5 cm.

B.T.—10 cm.

Thom's x-ray pelvimetry was performed with the following results: anterior posterior diameter, 11 cm.; transverse diameter, 13 cm.

The fetus was in left occipitoanterior position, and was thought to be normal in size. Since there was no apparent cephalopelvic disproportion, a trial of labor was decided upon.

On Oct. 12, 1944, the patient entered the hospital in labor. The membranes were intact, the uterine contractions were occurring every four minutes, the cervix was undilated and uneffaced. The head was dipping into the pelvis but was unengaged.

After eight hours of labor, with strong uterine contractions every three minutes, the cervix was still undilated and was noted to be in the posterior part of the pelvis. After ten hours' labor, the head had descended somewhat into the pelvis but was above the spines. The cervix was effaced and 1 cm. dilated. After fourteen hours of labor, the membranes ruptured spontaneously. The uterine contractions were of good quality. The cervix was 3 cm. dilated. The head was at the spines. By this time it was decided that vaginal delivery could be anticipated. After fifteen hours of labor, the cervix was 3.5 cm.



With the undilated, unyielding cervix pressed upon by the head, the active uterine segment pulls the inactive portion upward until finally a tear starts occurring at the cervicovaginal juncture, a line of cleavage develops, and continues until the separation is complete or practically so. A large portion retains a small attachment. A point of necrosis due to continued pressure on the cervix with ischemia is suggested, and this may occur. In our case there was no gross or microscopic evidence of such an area.

Five cases of amputation followed introduction of a rubber balloon. These cases perhaps should not be included in a report of spontaneous amputation of the cervix. Two were in cephalic and three in breech presentations. They, however, represent probable rigidity of the cervix in which the unyielding ring was pulled rather than pushed off from its original attachment.

### Summary

Annular detachment of the vaginal portion of the cervix during labor is a rare complication.

The basic causes for the condition are an unyielding cervix, disproportion, and a faulty mechanism of labor. The unyielding cervix develops a circular line of cleavage and is torn away at its cervicovaginal junctiva.

The fetal mortality has been extremely high (29 per cent). The high rate of stillbirths is due to the long labors, and the small pelvis, not cervical detachment per se.

In only one instance is spontaneous abortion mentioned as a sequel to cervical amputation.<sup>10</sup> One would expect this to occur more often following amputation of the cervix. Our experience with pregnancy following cervical amputation is that spontaneous abortion occurs frequently.

Four women here reported had successful subsequent pregnancies and vaginal deliveries. Gilles<sup>25</sup> patient had five normal deliveries later. DeCosta's<sup>1</sup> patient was later delivered by elective cesarean section. The indication for section was the former long difficult labor and the amputated cervix. An elective cesarean section is probably the best way to manage subsequent pregnancies. There will be exceptions to this rule.

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### Analysis of Reported Cases

1. Seventy-five per cent of the cases occurred in primiparas.
2. The average age of the patients was 31 years.
3. The length of labor was given in forty-one instances. The average length of labor in these was fifty-eight hours. The longest labor was one hundred eight hours, and a total of nine labors were eighty hours or longer. There was one eleven-hour labor.
4. Twenty-eight case reports stated that the membranes ruptured prematurely or early. This means at least an instance of 48 per cent early rupture of the membranes. Some reports made no mention of the membranes. There were but six cases where the membranes ruptured late in labor.
5. In nine of the 55 cases, the authors stated that the pelvis were contracted. In only six instances was "normal pelvis" definitely stated. This leaves forty cases where data upon the pelvis is not given. However, we note embryotomy listed under delivery in five cases where the size of the pelvis is not mentioned. This is suitable indirect evidence that contracted pelvis of some degree was present in another five cases, making a total of 14 cases, or over a 25 per cent instance of cephalopelvic disproportion.
6. The average weight of the babies, in 21 cases where those data were given, was 3,414 grams. Eight babies weighed 3,800 Gm. or more.
7. There were fifty-three vertex and two breech presentations, in both of which a rubber balloon was used.
8. Five cases of annular detachment of the cervix accompanied the use of an intrauterine hydrostatic bag. In the fifty remaining cases, spontaneous detachment occurred.
9. Seventeen authors made note of a "rigid cervix" to palpation, during the first stage of labor.
10. There were four maternal deaths in the series. Death followed infection in each instance. It is noted that these are mostly among earlier reports. An additional seven mothers (13 per cent) experienced stormy postpartum courses.
11. Postpartum bleeding occurred in eight cases. The excessive bleeding, seemingly, did not always arise from the cervix, but was secondary to uterine atony. It is remarkable that so few cases experienced excessive bleeding.
12. Sixteen stillborn infants are reported, a primary fetal mortality of 29 per cent.

### Discussion

Rigidity of the cervix is mentioned in seventeen cases, and in all cases reported the failure of the cervix to dilate normally is the outstanding feature. The characteristic doughnut-appearing detached cervix becomes amputated when the cervix is approximately 3 to 5 cm. dilated.

Many writers have postulated a primary cervical rigidity, and the fact that 75 per cent of the cases reported were in primiparas and averaged 33 years of age would suggest this possibility. On the other hand, histologic examination of many cervices show no primary structural differences from those of a normal cervix at term.

In 25 per cent of the cases reported, there was known cephalopelvic disproportion. This disproportion, with faulty mechanism of labor, we believe may cause secondary changes in the cervix which render it inelastic and unyielding. With impingement of the cervical tissue between the fetal head and the bony pelvis, congestion occurs with circulatory changes, leucocytic infiltration, and edema. Such changes were noted histologically in our specimen.

## SUBACUTE BACTERIAL ENDOCARDITIS DURING PREGNANCY

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**A**CUTE bacterial endocarditis developing during pregnancy is extremely rare. Stander notes in his book that a careful review of the literature reveals only 18 authentic cases. The introduction of penicillin has provided an effective means of therapy for this condition. The management of the pregnancy and this serious complication is of considerable interest to obstetricians and cardiologists. The careful reporting of individual experiences will provide some clinical data which may point the way to the most appropriate therapy.

The patient was first seen in her third pregnancy at about sixteen weeks. She was 31 years old and had two previous low or cervical cesarean sections for cephalopelvic disproportion in 1941 and 1943.

Her past medical history was essentially negative except for rickets. Her family history was irrelevant to her present complication. At the first prenatal examination all the physical findings, as well as the results of the laboratory procedures, were within normal limits. The only interesting finding was a high titer for brucellosis, 1:40.

The patient's prenatal course was uneventful until the pregnancy had progressed to about thirty-two weeks. She was spending the summer in upper Wisconsin and had a protracted sore throat which did not clear up on the usual medication. She was admitted to the hospital on Aug. 20, 1945, for study because of the following vague complaints: a feeling of lassitude, anorexia, night sweats, easy fatigability, epistaxis, roaring in the ears. The physical examination was negative except for the presence of a loud, harsh heart murmur replacing the first sound at the apex. This was not present at previous examinations.

The following studies were carried out at this time. Blood counts revealed a moderate anemia. In nose and throat cultures the usual flora was present with the exception of two colonies of *beta hemolytic Streptococcus*. The ear, nose, and throat consultants found an abnormal patency of the Eustachian tubes, probably associated with pregnancy, and an excoriation of the septal mucous membrane of the nose. The cardiologist thought that the heart murmur was associated with the anemia. An electrocardiogram revealed no pathology, but an x-ray of the chest for heart size showed it to be 40 per cent oversize. How much of this was the result of pregnancy could not be determined. It was thought that the high *Brucella* agglutinin titer, the opsonic index, and the phagocyte count were indicative of immunity rather than an active infection. Blood cultures for *Brucella* organisms and guinea pig inoculations proved negative subsequently.

The patient was discharged from the hospital unimproved for a few days during which she was asked to take her temperature every four hours. She continued to run a low grade temperature the level of which rose slowly so that she was readmitted on Sept. 4, 1945, for further study.

On September 11 the patient noticed that her finger tips had changed color, and she developed a transient numbness and tenderness. The heart murmur had become more pronounced. The size as measured by the x-ray had increased to 60 per cent above normal. Blood cultures were positive for the first

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### Penicillin Studies

The organism, *Streptococcus salivarius* was found to be sensitive to 0.02 units of penicillin per cubic centimeter. The dose of 125,000 units of penicillin every three hours maintained an adequate level for two and one-half hours after its administration; the level was 1.025 units per cubic centimeter.

At the time of delivery the following penicillin levels were computed:

Maternal blood	2.048 units per c.c.
Cord blood	0.512 units per c.c.
Amniotic fluid	4.096 units per c.c.

Samples of maternal blood, cord blood and amniotic fluid were taken at the time of delivery and cultured with and without a penicillinase (cysteine monohydrochloride). Aerobic and anaerobic cultures were negative after ten days' incubation.

On October 17, the penicillin level was 2.048 units per c.c. one and one-half hours after the administration of the last dose of 225,000 units, and this had dropped to 0.512 units per c.c. at the end of three hours. Penicillin therapy was discontinued on October 18. Arterial and venous blood cultures taken on October 25 and 30, November 5 and 9, and incubated for ten days were negative.

The patient has been well during the past year, although her activities have been restricted greatly. There have been no recurrences of the subacute endocarditis. The heart is enlarged and the findings are typical of mitral disease. Although she has made a spectacular recovery she did not escape serious residual cardiac damage.

### Discussion

The case history of a patient who developed subacute bacterial endocarditis during pregnancy is presented. The authors have not been able to find the report of a patient who developed this complication during pregnancy, survived, and subsequently gave birth to a living child. Undoubtedly, although this complication is encountered very rarely, the use of penicillin and streptomycin will improve the almost fatal prognosis for mother and child.

Treatment must be directed primarily to the eradication of the infection. However, the pregnancy presents special problems. In the past, therapeutic abortion was often advocated in order to improve the patient's ability to overcome the serious complication. Potent antibiotics which eradicate organisms from the bloodstream and keep it sterile, allowing the endocardium to recover from the infection, should make it possible to allow patients to continue their pregnancies to viability or longer. The eventual termination of the pregnancy can be carried out by the most appropriate method, but it must not be forgotten that the heart usually suffers irreparable damage. Delivery as well as subsequent childbearing must be considered in the light of the existing cardiac pathology.

Dr. Emmet Bay, Professor of Medicine, University of Chicago Medical School, was responsible for the medical management of this patient.

time and revealed a pure culture of *Streptococcus viridans* which was later identified as *Streptococcus salivarius* (Sherman classification). Repeat blood cultures on three successive days confirmed the diagnosis of subacute bacterial endocarditis.

She was started on penicillin therapy, receiving 125,000 units every three hours, or 1,000,000 units a day. Small blood transfusions were administered at frequent intervals. She became afebrile promptly and remained afebrile during her entire hospital stay, with the exception of the day following operation when the temperature rose to 37.6° C. The only noteworthy event occurred on September 17 when the patient complained of fleeting periods of amnesia, but these disappeared.

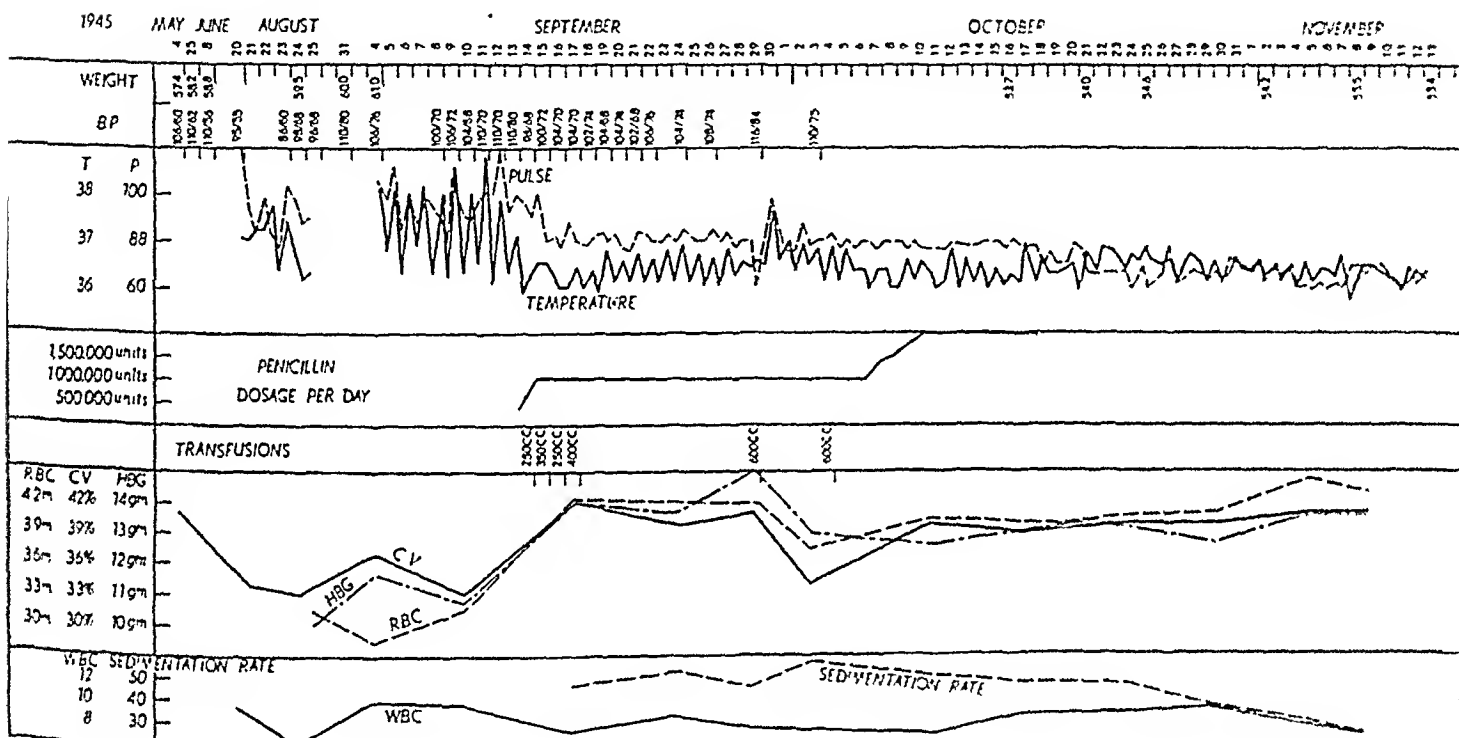


Fig. 1.

It was decided to terminate the pregnancy on Sept. 29, 1945. The baby was obviously viable, the active infection had subsided, and the heart would show no great improvement until the pregnancy was terminated. A cesarean hysterectomy was performed in order to decrease the hazard of postoperative infection and because this was her third abdominal delivery. She withstood the operation satisfactorily, and her recovery from this procedure was entirely uneventful.

A consultant who saw the patient suggested that the amount of penicillin be doubled, so that she received 250,000 units every three hours for the remainder of her treatment. Blood cultures, venous and arterial, sedimentation rates, blood counts were repeated at frequent intervals and can be followed in the graphic record.

Penicillin therapy was discontinued on October 18, the twentieth post-operative day and thirty-six days after it was started. She received a total dose of 45,850,000 units. The heart decreased in size slowly and the electrocardiogram showed a sinus arrhythmia and an occasional extrasystole. At the time of her discharge from the hospital on November 13, repeated arterial and venous blood cultures incubated for ten days were negative, the sedimentation rate was approaching normal, and the white count was normal.

cord blood gave a 1 plus Kahn and a slightly positive Kolmer, but mother and baby progressed normally.

Six weeks post partum the maternal serology was negative, and one month later the baby's blood was also negative both Kahn and Kolmer. At the same time x-ray examination of three extremities showed normal bone architecture and no evidence of periosteal reaction.

A recheck of the mother's chest likewise showed no changes as a result of her pregnancy or anesthesia.

While continued observation has been advised, it now seems quite probable that both mother and baby are free of syphilis.

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## SYPHILIS IN PREGNANCY TREATED BY PENICILLIN\*

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SINCE the publication in 1943 by Mahoney<sup>1</sup> of the first use of penicillin in the treatment of syphilis, there have been many carefully controlled studies using this agent in practically all branches of syphilotherapy. In the field of prenatal syphilis there have been at least three reports of detailed treatment and results.<sup>2-4</sup> Since the total number of cases reported to date has been small, it was felt that the following should be presented.

Mrs. G., aged 27 years, was first seen when three weeks past her first missed period. She had had a left pneumothorax for three years for pulmonary tuberculosis, and was attempting a pregnancy with the consent of her physician. Since the pelvic findings were not conclusive, she was given some dietary instruction and told to return in three weeks. At the second visit the pelvic findings were more definite, and, other than her left pneumothorax, physical examination was essentially negative. A blood sample at this visit was reported Rh positive, Group O, Kahn 3 plus. On the basis of the latter a second sample was sent to a second laboratory which reported Kahn 4 plus, Kolmer strongly positive. Her husband saw his physician and was told that his blood also was 3 plus.

Lacking any other findings than positive serology, having a history of a negative Kahn at the time of the original pneumothorax, and a husband just returned from overseas service, it was felt that this was a case of an early latent syphilis. This was strengthened by the history of penicillin therapy two months before for a dermatitis. Fearing the result of heavy metal therapy upon the tuberculosis, it was suggested that we abort her to avoid a syphilitic baby. As such a course would still leave an infected mother, we decided to try penicillin first, deferring the abortion until there might be evidence of its failure. Consequently, she received 2,400,000 Oxford units of the sodium salt in eight days. Ten days later the second laboratory reported the Kolmer still strongly positive, but the Kahn had dropped to a 3 plus. Another month later the Kolmer was clearing in the fifth tube and the Kahn had dropped to 2 plus. Fetal movements were first felt at about this time.

In a discussion of the case with a dermatologist, her physician was given a very gloomy prognosis, and a second course of treatment combining heavy doses of both penicillin and mapharsen was advised. In a desperate quandary, a summary of the case was sent to Dr. John H. Stokes. His prompt reply<sup>5</sup> gave the opinion that the baby would be normal and that probably we had also cured the mother's syphilis. A note of caution was sounded in a subsequent communication in which attention was called to the fact<sup>6</sup> that the newer penicillin is much less effective against the *treponema pallidum*, and suggested a second and heavier course of treatment in the event that quantitative Kahns failed to show steady improvement.

Following his suggestion, seven weeks from the end of treatment, a quantitative Kahn was 4 units, while the Kolmer did not go beyond the first tube. Meanwhile the pregnancy progressed uneventfully, and two months later a completely negative quantitative serology was reported.

A living female infant weighing well over 8 lb. was delivered by low forceps at term under nitrous oxide, oxygen, and a total of two ounces of ether. The

\*Presented before the Pittsburgh Obstetrical and Gynecological Society, Dec. 9, 1946

mediately. On questioning the patient she stated that for several days preceding this bleeding she had been entertaining friends from out of town and had been riding a good deal in automobiles and was obtaining very little rest or sleep. At the hospital she was placed on a regime of absolute rest in bed, large doses of progesterone, vitamin E, and sedation. The bleeding subsided and the patient appeared to be doing well, when on the ninth day in the hospital labor began and she was delivered of fraternal male twins at twenty-four weeks of pregnancy, on Feb. 20, 1946. The first infant weighed one pound, ten ounces, and the second baby weighed one pound, eleven ounces. The second twin lived only two hours, and the first twin survived for ten hours. The mother made an uneventful recovery.



## TUBAL AND UTERINE TWIN PREGNANCY\*

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**T**HIS case is being reported because it is unusual and rare. I have been unable to find any similar reports in the recent literature or in the standard textbooks.

Mrs. L. D., aged 35 years, gravida iv, para i, Rh positive. Menstrual periods occurred regularly every twenty-eight days, lasting three days, without dysmenorrhea. She had a right inguinal herniorrhaphy performed in April, 1937, and two years later in May, 1939, an appendectomy. On Jan. 31, 1941, she was delivered of a living male child by a Seanzoni maneuver after a twenty-hour labor with a persistent posterior head. Her convalescence was uneventful. During her second pregnancy she miscarried at two months, and a curettage was performed in September, 1943. The following year, in September, 1944, during her third pregnancy, she ruptured the membranes at twenty-six weeks and promptly started in labor and was delivered of male fraternal twins weighing two pounds, four ounces, and three pounds, two ounces, respectively. They survived approximately seventy-two hours.

In this present illness her last regular period had occurred on August 24, 1945. Six weeks later, on October 6, 1945, at 11:30 P.M., I performed an emergency operation at the Carney Hospital, removing an unruptured left tubal pregnancy. There were about 5 c.c. of free blood in the pelvis which had apparently leaked out through the fimbriated end of the tube. The right tube was normal, as were both ovaries. The pathologic report was: "Ectopic tubal pregnancy; chorionic villi showing regressive changes, trophoblastic giant cells with massive hemorrhage, and an acute inflammatory reaction in the wall of the tube. There is no evidence of malignancy."

At the time of the operation I observed that the uterus was slightly enlarged and made a note of it in the operative procedure. Her convalescence was uneventful except for the fact that she complained of more nausea than is usual postoperatively for an otherwise uneventful course. She was discharged home on the eleventh postoperative day.

Pelvic examination one month later at the office revealed a uterus enlarged to the size of a two months' gestation, although she had had no marital relationship since some time before the recent operation. She had not menstruated since her last regular period August 24, 1945. A Friedman test at this time was reported positive, confirming the diagnosis of intrauterine pregnancy.

She was placed on the usual prenatal regime with additional advice to have rest periods and to take special care to avoid overexertion of any type. Progesterone and vitamin E were also prescribed because of her past history.

In the latter part of January, 1946, when she was about four and one-half months pregnant, she was x-rayed for the possibility of twins because the uterus appeared to be larger than was consistent with her period of amenorrhea. X-ray confirmed the diagnosis of intrauterine twin pregnancy. About two weeks later she began to stain and then began to flow slightly. She was hospitalized im-

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## TRUE KNOT IN THE UMBILICAL CORD CAUSING DEATH OF MONOAMNIOTIC TWINS IN A PRIMIPARA BEFORE LABOR

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MRS. E. R., a 20-year-old para 0, gravida i, was first seen by one of us (J.B.B.) on Mar. 16, 1942, stating that her last menstrual period had occurred on Nov. 20, 1941. Physical examination confirmed the diagnosis of pregnancy, and the date of confinement was estimated to be Aug. 27, 1942. No physical abnormalities could be found, and pelvic measurements were within normal limits.



Fig. 1.—Stillborn, macerated monoamniotic twins showing knotted cords causing death.

The prenatal course was uneventful until April 21, when slight spotting of blood appeared, and ceased with bed rest and sedation. Fetal movements were noticeable after four and one-half months. On June 30, there was an increase of blood pressure which fluctuated for the next two weeks between 134/94 and 140/100, with a trace of albumin present. With this increase of pressure heart sounds became inaudible. Examination every few days thereafter failed to reveal evidence of fetal life. On July 6, a flat plate of the abdomen showed twins in the vertex presentation.

The patient was admitted to the hospital on July 12 with irregular abdominal pains. There were signs of mild toxemia, her blood pressure was

## MARGINAL PLACENTA PREVIA TREATED BY ARTIFICIAL RUPTURE OF THE MEMBRANES THIRTY-NINE DAYS BEFORE VAGINAL DELIVERY

ROBERT S. MILLEN, M.D., WESTBURY, N. Y.

*(From the North County Community Hospital)*

**I**N THE following case a marginal placenta previa, diagnosed at twenty-eight weeks, was treated by rupture of the membranes, and the patient delivered vaginally thirty-nine days later. The 5 lb., 4 oz. baby lived.

The patient; a 35-year-old multipara, whose past history included a nephrectomy in 1940 for a tuberculous kidney, was delivered of her first infant as a normal primipara in January, 1945.

The present pregnancy, which was expected to be at term on July 17, 1946, was normal until she was approximately twenty-one weeks, at which time vaginal bleeding occurred at the end of a strenuous day. All bleeding ceased after bed rest for forty-eight hours. One week later she was allowed up progressively, only to have spotting occur after she had been out of bed seven days. The next three weeks, one in bed and two up, she was symptom free. Spotting then occurred. The patient was put back to bed. After she had been confined to her bed for two weeks profuse vaginal bleeding occurred, unaccompanied by pain on exertion. She was immediately hospitalized, as the length of her pregnancy and type of bleeding indicated a tentative diagnosis of placenta previa. As x-ray studies failed to locate definitely the placenta in the fundus, a pelvic examination was done. A vertex was presenting and dipping into the pelvis. The cervix was moderately thick, but admitted one finger. A marginal placenta previa was noted. Because of the unlikelihood of the baby surviving, the location of the placenta, the amount of bleeding which she had already had, and the type of cervix, it was deemed advisable to rupture the membranes. Two doses of infundin (one minim each), twenty minutes apart, produced some mild cramps and controlled the bleeding. Twenty-four hours later, when the patient had not gone into labor, but the bleeding was satisfactorily controlled, it was decided to attempt further induction by castor oil, rather than run the risk of a violent labor with more infundin. A cathartic effect was obtained, but no labor was forthcoming. The patient, therefore, was started on penicillin 20,000 units every three hours as a prophylactic measure. This was stopped after two afebrile weeks. During the thirty-nine days following the rupture of her membranes the patient continued to leak amniotic fluid, and on four occasions had a slight amount of bleeding, varying from a dram to half an ounce. Each time it was readily controlled with one dose of one minim of infundin. Frequent blood studies were made and four transfusions, as well as iron by mouth, were used to support her blood level. She had an easy two-hour and thirty-minute labor, being delivered under pudendal block anesthesia with low forceps, as the baby's head arrived on the perineum.

## Editorial

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### The Third American Congress of Obstetrics and Gynecology

The JOURNAL is pleased to announce the holding of a Third Congress devoted to the progress of this branch of medicine to be held in St. Louis, Mo., on Sept. 8 to 12 of the current year. In an editorial published in the February, 1937, issue, the attention of the profession was called to the need and desirability of holding such a Congress in a field to which American physicians and institutions had contributed so much and which should afford an opportunity for the inter-exchange of ideas, for the presentation of advances in methods and techniques, for the instruction of visitors, be they physicians, nurses, public health officials, for the display of scientific achievements and research products, for commercial exhibits. Two very successful and well-attended Congresses have been held, the first in Cleveland in 1939, the second in St. Louis in 1942. Both were sponsored by the American Committee of Maternal Welfare, as is the Third Congress now in process of formation. It promises to be equally successful. Committees have been organized to arrange the necessary details, and the programs thus far developed promise much of value to those who will attend the sessions. It affords unexcelled opportunities for instruction, for entertainment, for a gathering of minds.

Interest in the welfare of womankind is age-old and worldwide. No longer is such interest based merely on sentiment, on religion, on conventional standards; it depends today on knowledge and reason. That particular branch of medicine which is concerned with the productive life of women has grown and developed enormously in these last hundred years, but it has also involved and invaded many allied fields. These strides in medical and social progress may justifiably be recorded and disseminated through the medium of a National Congress to which the JOURNAL is prepared and desirous of giving its unqualified support.

135/95, with slight ankle edema, and a trace of albumin in the urine. The presenting part was unengaged, and fetal heart tones could not be located. X-ray of the abdomen at this time revealed overlapping of fetal skull bones. Treatment with bed rest, sedation, salt-free diet, and concentrated glucose resulted in recession of pressure, edema, and albuminuria. On July 14, a medical induction by castor oil, enema, and quinine was instituted. Gradually the pains became regular and labor progressed. At 7:00 A.M. on July 15, the membranes ruptured, and at 7:45 A.M. the first twin was delivered spontaneously in left occipito-anterior position, and five minutes later the second twin in right occipitoanterior presentation. Both were males, and were discolored and macerated, having apparently been dead for some time. The placenta separated spontaneously and delivered immediately. There was but one placenta with two cords, the middle thirds of which were intertwined and knotted, causing a cluster of knots the size of one's clenched fist.

The postpartum course was uneventful, and the mother was discharged on her seventh postpartum day.

### Comment

We felt this case unusual and worth reporting inasmuch as it falls into that rare group of monoamniotic and uniovular twins, and in a primigravida prior to the onset of labor. The incidence of monoamniotic twins has been variously estimated by Müller at 1:6,000, and by Rosenberg at 1:60,000. In a review of the literature Quigley was able to find only 109 cases; torsion or true knot formation was reported 58 times, or in 53.2 per cent. Lundgren found 24 of 31 reported cases to be associated with multiparity. McNally has called attention to the misconception that fetal death occurs only during labor. Most writers on this topic are of the opinion that knotting occurs at the ninth to twelfth week of gestation, at which time the cord is sufficiently long and the fetuses small and active. The knots are tightened during labor, resulting in impairment or complete blockage of the fetal blood supply. Several authors comment on the formation of a knot in the cord of a second twin by delivery of the first.

There is little or no risk to the mother; however, Quigley mentions eclampsia four times in his 109 cases; both McNally's and our own case, in which the fetuses died prior to labor, were mildly toxie.

The separate cords of twins are especially adapted to intertwining and knotting if present in one amniotic sac. Atwood is of the opinion that knots formed during delivery are never serious—those formed early in gestation may prove fatal. In Quigley's series (109 cases), both twins survived in only 17 cases. Both twins died in 41 cases, and one died in 20 cases. Eight monsters died, the result in 23 was unreported, and 8 aborted, leaving 94 cases from which to estimate mortality. One hundred twenty-six fetuses of 94 twin pregnancies did not survive, leaving a 68 per cent mortality.

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## Analgesia, Anesthesia

de Senarclens, Francois: The Effect of "Dolantine" Upon Delivery, *Gynaecologia* 121: 225-246, 1946.

Senarclens, of the St. Gall Obstetric Hospital, describes his experience with the intramuscular injections of 100 mg. of "Dolantine" (known as demerol in America), chemically the hydrochloride of 1-methyl 4 phenyl piperidine 4 carboxyl acid ethyl ester.

Dolantine is given at the onset of labor and repeated, if necessary, four hours later (seven cases). The author's series includes 167 cases, 127 primiparous and 40 multiparous. Sixty-one patients were less than 25 years of age; 85 cases, 26 to 35 years of age, and 21 had passed their 35th birthday.

The author states that pains were regular in type in 81 per cent of the cases, mediocre or poor in the remaining 19 per cent. The intensity of the contractions were classified as feeble in 8 per cent, average in 58 per cent, and strong in 3 per cent. The remaining 31 per cent were categorized as irregular. There was increased duration of labor pains in 10 per cent, no change in 44 per cent, and a decrease in duration in 33 per cent of the cases, while 3 per cent exhibited arrested contractions. The expulsive pains were considered good in 76 per cent, fairly good in 10 per cent, and poor in 14 per cent of the cases. The average duration of labor for the primipara group was fourteen hours, twenty-five minutes; while the multipara duration of labors averaged eight hours, fifty-five minutes.

Three per cent of the cases were subjected to cesarean section, 6 per cent to forceps delivery, and 4 per cent to trachelotomy among the obstetrical interventions. In 58 per cent of the cases the perineum required operative care—episiotomy in 30 per cent, repair of first degree tear in 10 per cent, and a second degree tear in 8 per cent.

Seventy-two per cent of the cases delivered their placentas normally; 23 per cent required fundal pressure—while six cases required manual removal. The blood loss was 500 Gm. or less in 78 per cent of the cases; 10 per cent lost 510 to 1,000 Gm.; 3 per cent lost 1,010 to 1,500 grams.

Febrile complications were present in 35 per cent of the cases (4 per cent febrile; 3 per cent endometritis; 7 per cent subinvolution; lochiorrhea, 2 per cent; mammary engorgement without abscess, 4 per cent; thrombosis, 2 per cent. There was one death of septicemia occurring eleven hours after delivery. Posterior pituitary extract solution was used intrapartum in 13 per cent of the cases, quinine in 7 per cent. Eighty-two per cent of the newborns were normal, and 2.25 per cent were "a little sleepy"; 6 per cent had asphyxia levida, and 2.25 per cent asphyxia pallida. Three per cent of the babies were born dead (2 macerated and 3 stillbirths) and an additional 2.25 per cent died in the neonatal period.

The author concludes—"the normal labor of the primipara and the multipara is relieved, accelerated, and rendered less painful" when "Dolantine" (demerol) is used. This drug was found most valuable in cases exhibiting pelvic disproportions where it exerted an effect similar to opiates but did "little harm to the mother and child."

C. E. FOLSOME.

Sauter, Hans: The Effect of a Spasmolytic Used in the First Stage of Labor. Investigation of a New Drug, "Hexacompal," *Gynaecologia* 121: 247-268, 1946.

Sauter investigated a new spasmolytic preparation "Hexacompal" (a suppository containing paverine HCl 0.025, extract of belladonna 0.05, Allobarbitol 0.05, dimethyl amino antipyrine 0.30, and caffeine 0.30). He compared this preparation to spasmalgin (a combination containing paverine HCl 0.020, pantopan 0.01, and atrinal 0.001) and dolantine (known in America as demerol). The latter two are administered by intramuscular injection. The writer reports a much more improved uterine tone, with relief of spastic conditions and acceleration of the first stage of labor from the use of hexacompal as compared to the other two drugs.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Malignancies

Gray, Layman A., Friedman, Milton, and Randall, William F.: Observations on Treatment of Adenocarcinoma of the Uterus, Surg., Gynec. & Obst. 82: 386, 1946.

Ten women suffering from adenocarcinoma of the uterus are presented without five-year follow-up. Six out of seven of the patients still had residual carcinoma at hysterectomy, in spite of the fact that they were treated with large doses of intrauterine radium; and three of these patients had metastases to the ovary, indicating the necessity for oophorectomy at the time of operation. The authors describe an instrument for application of intrauterine radium tubes which is designed to make the radium more effective. This instrument, termed by them a hysterostat, makes possible the placing of the tubes both transversely and in lateral tandems. Of the ten patients treated, seven received extremely large doses of radium, namely, 6,030, 7,000, 7,000, 8,000, 8,900, 10,410, and 12,480 milligram hours. Hysterectomy followed the application of radium in thirty-eight days to six months. Six of these seven uteri showed residual carcinoma. The seventh showed no evidence of tumor and was the case treated with 12,480 milligram hours. Three of these patients had ovarian metastases. The authors conclude that radium alone is not sufficient to cure adenocarcinoma of the uterus. They are unable to state the exact role and specific indications for preoperative radium therapy.

L. M. HELLMAN.

Rojas, Daniel A.: Dysgerminoma of the Ovary, Bol. Soc. de obst. y ginec. de Buenos Aires 25: 33-56, 1946.

The author reports four cases of dysgerminoma of the ovary. Three of the patients were under 20 years of age, and one was 26 years old. In all of the patients menstruation was normal, and there were no abnormal symptoms. Three of the patients were virgins, and the fourth patient had previously had two children. In one of these labors she had dystocia because of the ovarian tumor.

Laboratory studies before operation revealed no special information. In three of the four cases a supravaginal hysterectomy was performed with removal of both adnexa. In one patient only the ovarian tumor was removed.

J. P. GREENHILL.

Nestarez, Oscar B., and Assali, Nicolau S.: Some Aspects of Cancer of the Endometrium: Its Association With Pregnancy, Obst. y ginec. latino-am. 4: 161-189, 1946.

Cancer of the body of the uterus is more frequent after the menopause. Pregnancy does not seem to have any effect on the development of cancer of the body of the uterus; neither do fibromyomas. On the other hand, glandular hyperplasia of the endometrium seems to have a connection with this type of cancer, particularly when it occurs during or after the menopause. The authors report a case of epidermoid cancer of the endometrium associated with pregnancy which was removed by means of curettage. They also report two cases of epidermoid metaplasia of the endometrium with beginning malignant degeneration in the first and polypoid hyperplasia with a malignant tendency in the second.

The authors mention that there are in the literature eight cases of cancer of the body of the uterus associated with pregnancy, including their own case.

J. P. GREENHILL.

than palliation occurs, for there is a definite arrest, if not regression of the disease. Side effects are rarely sufficient to require that the treatment be abandoned. A daily dose of 1 to 5 mg. has been used. The mode of action is unknown. The changes in serum level of acid phosphatase would indicate an interference with the metabolism of the malignant cells. Huggins felt that if the activity of estrogens in the malignant cells of the prostate could be inhibited, then the growth of primary and secondary tumors would regress.

L. M. RANDALL.

White, Abraham: Preparation and Chemistry of Anterior Pituitary Hormones, *Physiol. Rev.* 26: 574-608, 1946.

White of Yale re-evaluates the anterior pituitary hormones. Upon the basis of physiologic evidence he states that there appear to be at least six recognized individual hormones, although there exists some biological overlapping among certain of the anterior pituitary secretions. Four of these protein hormones have been isolated in a homogeneous and highly purified state through the application of protein chemical techniques. These four include the lactogenic, the adrenotrophic, the growth, and the luteinizing hormones. The thyrotrophic principle has been isolated in highly purified form, but has not been examined by rigid criteria of protein purity. The follicle-stimulating hormone awaits further purification.

The author is of the opinion that success in the isolation and characterization of these anterior pituitary hormones has been related to advances in knowledge of protein chemistry. He states the biological activity seems to be intimately related to the protein nature of the active principle, and procedures which alter the protein structure even slightly result in a partial or complete loss of physiologic characteristics. A notable exception is the adrenotrophic hormone.

Efforts to detect in the protein hormones nonamino acid groups or active groupings of amino acids to which hormonal function could be assigned have been unsuccessful. At least three of the active principles, i.e., the thyrotrophic, the follicle-stimulating principle, and the luteinizing hormones contain carbohydrate in their structure. The inhibition of hexokinase by crude anterior pituitary extracts suggests the possibility of an important test system, by the use of both purified proteins and of models of known structure. This approach would be possible to the problem of the relation of protein structure to hormonal action.

White concludes that certain physical and chemical differences exist among anterior pituitary hormones isolated from different species. These variations are most striking by a comparison of the data for the luteinizing hormone preparations obtained from hog and sheep pituitaries; beef and sheep thyrotrophic hormonal proteins seem to be different. There exist also slight variations in the lactogenic hormones from beef and sheep glands. On the other hand, the purified hog and sheep adrenotrophins, although isolated by different techniques, appear to be identical in every property examined.

C. E. FOLSOME.

Munro, S. S., and Kosin, Igor L.: Relative Potency of Certain Synthetic Estrogens When Administered Orally to Chicks, *Am. J. Physiol.* 147: 582-590, 1946.

The authors evaluated the relative estrogenic potency of six synthetic estrogens biologically in young white Leghorn chicks. The estrogenicity of these compounds apparently increased with increasing saturation in the aliphatic block of the molecule (i.e., "open chain" portion of the molecule) and with methylation of the side chains (addition of methyl groups,  $\text{CH}_3$ ).

The descending order of potency of the six compounds within the dose range used, three levels of 10, 20, and 30 mg. per pound of mash feed, was as follows: dianisylhexane (dimethyl ether of hexestrol), dianisylhexene (dimethyl ether of diethylstilbestrol), hexestrol, dienestrol, dienisylhexadiene (dimethyl ether of dienestrol), diethylstilbestrol.

The writers found that the degree of variability in oviduct response rose with the increased dose level of estrogens. They observed also that the growth rate of chickens greatly



The author found hexacompal suitable for tests of uterine contractility in early labor. He observed no untoward secondary manifestations from the drug's use. The contraindications and comparative considerations are detailed, including its use after thymophysin.

C. E. FOLSONE.

Collins, Selwyn B., Phillips, F. Ruth, Oliver, Dorothy F., with collaboration of Hingson, R. A., Vaux, Murray, and Lull, Clifford: A Statistical Study of Delivery With Continuous Caudal Analgesia as Compared With Other Methods, Pub. Health Rep. 61: Nov. 29, 1946.

This paper contains a detailed statistical analysis of the deliveries of 2,516 mothers under continuous caudal analgesia at the Philadelphia Lying-In Unit of the Pennsylvania Hospital during the period from May, 1943, through August, 1945. One thousand twenty-four deliveries by other than continuous caudal analgesia occurring during the period from December, 1942, through July, 1943, served as a control group. Although the control series is almost half the size of the caudal series, the distribution according to age and parity, complications, and type of delivery of the two series seems to be similar. It is to be noted, however, that the incidence of complications during delivery and the incidence of prolonged labors were slightly higher in the control than in the caudal group. Ninety and four-tenths per cent of the mothers in the caudal group received complete relief from pain, 4.3 per cent partial relief, and in only 5.3 per cent was there a failure of the method to relieve pain. The average duration of the caudal analgesia for primiparas was 3.7 hours, and 2.3 hours for multiparas. Drop in blood pressure of over 25 mm. occurred in 33.5 per cent of these mothers. There were two maternal group deaths in each group. Unfortunately, the details of these maternal deaths are not given. It is of interest to note that the incidence of mid-foreeps is 8.4 per cent in the caudal group, while it is only 4 per cent in the control. Duration of the third stage was significantly shortened in the caudal group, and the incidence of febrile puerperium and subinvolution was also significantly reduced in the experimental cases. Of most marked interest, however, is the fetal outcome in these patients as compared with the control series. The percentage of infants who required a special agent to induce respiration was significantly reduced in the caudal group and, although the per cent net gain in weight by the seventh day was not significantly greater in the caudal cases, it did show some increase which indicated a trend. In the caudal group the stillbirths amounted to 9.1 per thousand live births as compared with 24.8 per thousand for the control. Similarly, the neonatal deaths were 11.5 per thousand live births in the caudal group as compared with 20.8 per thousand in the control. Thus, the total stillbirths and neonatal deaths were 20.6 per thousand in the experimental group as compared with 45.6 in the control. This is definitely a significant difference. The difference in stillbirths and neonatal mortality rates between the caudal and control group is still significantly different when the infants are divided into full-term and premature infants.

L. M. HELLMAN.

## Endocrinology

Dodds, E. C.: Estrogens in Cancer, Schweiz. med. Wchnschr. 842: number 37/38, 1946.

The author briefly reviews the development of potent substances with estrogenic properties, both natural and synthetic. The latter includes stilbestrol, hexesterol, and dienestrol.

Huggins was the first to administer stilbestrol to patients suffering from cancer of the prostate. Other workers have confirmed the fact that about 95 per cent of these patients will respond in some degree to treatment, experiencing relief of pain due to pressure on nerves and frequently to urinary obstruction; likewise the level of acid phosphatase is reduced. There usually results an improvement in the patient's general condition, and in some cases a reduction in the size of the primary tumor and the secondary deposits. One does not claim synthetic estrogens to be a cure for cancer of the prostate; however, more

preferentially by the genital tissues. It appears likely that estrogens may be used for the correction of pathologic changes in the skin other than those directly caused by estrogen deficiency.

EDWARD C. HUGHES.

## Endometriosis

Kahanpää, V.: Upon the Pathogenesis of Ovarian Endometriosis, Acta obst. et gynec. Scandinav. 26: 139-160, 1946.

Kahampää describes in considerable detail the histopathologic findings of operative specimens taken from six cases of ovarian endometriosis and hemorrhagic cysts on the Second Women's Clinic at Helsinki.

The author agrees fully with Sampson's observations and opinion as to pathogenesis. However, he stresses the importance of follicular rupture and extravasation of blood in tissues in the development of a superior substrate for the subsequent implantation and survival of endometrial tissue fragments. His studies agree unusually well with similar findings, on the latter aspect, of Philipp and Huber.

The writer concludes that his 15 photomicrographs and studies showing evidence of better substrate to the subsequent growth of misplaced endometrial cells eventuating in ovarian endometriosis constitute valuable and substantial proof toward further confirmation of Sampson's implantation theory.

C. E. FOLSOME.

Fallon, John: Endometriosis in Youth, J. A. M. A. 131: 1405, 1946.

The author reports nine cases of endometriosis in teen age girls among the last 225 patients with proved endometriosis who were seen in the Fallon clinic (4 per cent). The youngest was 13 years of age.

The cardinal symptom was increasing dysmenorrhea.

The diagnosis of endometriosis should enter into the differential diagnosis of abdominal pain as soon as menstruation has been established. The author emphasizes the fact that endometriosis is a sterilizing disease, and tends to occur after about five years of incomplete sexual function, that is, menstruation without pregnancy, and these years are most likely to be the first five after the onset of menstruation.

The authors advise that menstruating females who are being operated upon for appendectomy should be operated through a median incision to allow light enough for inspection of the deep pelvis.

WM. BERMAN.

Yin, Y. C.: Endometriosis and Adenomyosis, West. J. Surg. 54: 490, 1947.

Endometriosis and adenomyosis are thought to be of different origins. They differ slightly also in histopathology and symptomatology. Both conditions are activated by high estrogen levels in the blood. It is suggested, and a case report demonstrates the validity of this suggestion, that the complete removal of one ovary and resection of most of the opposite ovary may result in involution of the implants.

The author feels that implantation occurs as the result of reflux menstruation, and that in such cases implantation is favored by high estrogen levels. In adenomyosis it is felt that the aberrant tissue is congenital in origin.

WILLIAM BICKERS.

## Gynecology

Sauramo, Hannes: On Ovarian Hemorrhages With Special Reference to Intra-Abdominal Hemorrhages From the Corpus Luteum, Acta obst. et gynec. Scandinav. 26: 105-118, 1946.

Sauramo, of the Second Women's Clinic, University of Helsinki, reviews Bauman's 300 cases of ovarian hemorrhage, collects 292 additional cases from the literature and adds 2 cases of his own. In the one case the patient experienced a severe intraabdominal hemorrhage from

affected the degree of oviduct response. They stressed need for adequate numbers of test animals and the necessity of several dosage levels when using this bioassay method to compare the potency of estrogens.

C. E. FOLSOME.

**Tschumi, Rene:** The Influence of Vitamins and Endocrines Upon the Physiology of Sperm Motility, *Gynaecologia* 121: 169-203, 1946.

Tschumi, working in Joels laboratory and the Women's Clinic at Basel University, contributes observations upon the direct influence of certain compounds upon human sperm motility. Among the substances used were certain vitamins: thiamine, riboflavin, pyridoxine, nicotinamide, ascorbic acid, and sodium tocopherol phosphoric acid esters; certain endocrine agents, thyroxin and posterior pituitary solutions; and, also the chemical intermediary acetylcholine.

The author adds pertinent data on sperm suspension substrates through his comparative evaluation of isotonic Ringer's solution and Baker's solution besides observing, in addition, the influence of dilutions of each of the above compounds in concentrations of 0.001; 0.01; 0.1 and 1.0 per cents using Baker's solution as the control in each experiment. In the forepart of his paper, Tschumi outlines his detailed methods using sperm from 12 males, aged 24 to 39 years. He reports that motility is prolonged upon the dilution of isotonic saline and glucose solutions, and the quality of motion is improved.

Baker's solution was found more useful as a sperm suspension than Ringer's solution; the former produced unusual improvement in motility, increased the number of motile sperm, and, in some instances, prolonged the motility as long as 700 hours, while Ringer's solution served primarily as a preservative substrate. Daylight exerted a shortened ability of sperm migration in a specially devised capillary tube as compared to sperm migrating upon the tubes in darkness—an important observation for future workers to remember. The elevation of the substrate to body temperatures decreased the sperm migration in capillary tubes but increased the intensity of motility.

Thyroxin, nicotinamide, and vitamin E, and, to a less extent, thiamine, all seemed to exert a tendency to favorably increase the distance travelled by sperm while ascorbic acid, acetylcholine, and posterior pituitary solutions seemed to exert no effects. The riboflavine and pyridoxine demonstrated an inhibitory effect upon motility. The article is well documented with 20 graphs and four tables.

C. E. FOLSOME.

**Goldzieher, Max A.:** The Effects of Estrogens on the Senile Skin, *J. Gerontology* 1: 196, 1946.

According to observations made previously by other investigators, topical application of estrogen has been known to prevent genital atrophy and to restore the normal state of the mucous membranes of the external genitals. In view of these experiments, the author has determined the effect of estrogen in an ointment base on restoring normalcy to the senile skin. The experiments were carried out on five elderly patients using estradiol and diethylstilbestrol and compared with three additional patients as controls. In two cases, the potency of the ointment used assayed at 10,000 I.U. of estradiol per ounce. In the other three patients, one miligram per ounce of diethylstilbestrol was administered. The hormone-containing ointment was rubbed in by gentle stroking daily for five minutes over a period of six weeks. Biopsies of skin were studied in the five cases to compare the structure of the aged skin before and after topical application. The treated skin showed pronounced regeneration of the surface epithelium. The number of cell layers was increased, and the wavy configuration of the epidermis was restored. The water content of the estrogen-treated skin appeared greater, and the elastic fibrils were more numerous. Biopsies from the skin of the control group showed no appreciable changes. The author feels that topical application affects the skin to a much greater degree than oral or parenteral application because the estrogen is not lost through body excretion, is not deactivated by the liver, and is not used

# Correspondence

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## Anteversion of the Retroverted Uterus

*To the Editor:*

In his article on the procedure for anteversion of a retroverted uterus in the November issue of the JOURNAL, Dr. Carl T. Javert states, "The importance of correction of malpositions of the uterus is beyond the scope of this article, yet the improved chances of conception, prevention of spontaneous abortion, relief of nausea in pregnancy, alleviation of backache, and treatment of the incarcerated pregnant uterus are acceptable indications."

Is it true that the above are acceptable indications for the replacement of a retroverted uterus?

1. What proof is there that in a woman who has never been pregnant anteverting the uterus will help her to become pregnant? Although I have known a woman who has had a child become pregnant after anteverting her uterus, I have never known sterility to be cured by this device in a woman who has never been pregnant.

2. Is there any real proof that spontaneous abortion is the result of retroversion? This idea was once held, and passed on from textbook to textbook, but my own impression is that, allowing for the ratio of retroversion to anteversion in the female public, spontaneous abortion is no more common with retroversion than with anteversion.

3. It used also to be taught in the textbooks that nausea of pregnancy could be caused "reflexly" by a retroverted uterus. Is this idea still held by anyone with experience? If so, what is the proof?

4. Does anteverting a retroverted uterus cure backache? Very occasionally backache that is strictly localized over the "gynecologic" area may be cured by this procedure—but how often is even "gynecologic" backache cured by it?

5. In approximately 4,000 obstetric cases I have seen only an incarcerated retroverted uterus once. Is it therefore good obstetrics to antevert all the retroverted pregnant uteri that present themselves because one in 4,000 will become incarcerated.

I have for some time been warning my students against the temptation that will beset them after graduation to join with their brethren in doing their share of the really atrocious number of useless suspensions at present being done. But when they can go to the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in their library and see the printed word that I have quoted from Dr. Javert above, of what avail my warning?

H. B. ATLEE, M.D.

118 SOUTH PARK STREET,  
HALIFAX, N. S.  
DEC. 9, 1946.

## Reply by Dr. Javert

*To the Editor:*

The focal point of the article in question is clearly stated in its title, and is elaborated in the text. An illustration was presented for further emphasis. Dr. Atlee ignores the theme of the article which deals with a method and concentrates on one sentence regarding "acceptable indications" for use of the method. Realizing the controversial nature of these indications and wishing to avoid a discussion of them, the writer stated that their importance was "beyond the scope of this article."

a ruptured corpus luteum cyst on the 21st day of a cycle. The second case was also accompanied by severe shock from rupture of corpus luteum cyst, crow-egg size, occurring on about thirtieth day of the cycle. In the collected 292 cases the author reports a mortality of 0.7 per cent.

C. E. FOLSON.

**Kleitman, R.: On the Question of Disgerminoma Ovarii, Robert Meyer Type, Acta obst. et gynec. Scandinav. 26: 85-104, 1946.**

The author reviews three cases of disgerminoma ovarii, R. Meyer, observed during the past thirteen years at the Gynecology Clinic of the Public Maternity Hospital, Stockholm.

One case, incompletely operated upon, and treated with radiation therapy, died two years later. A second case submitted to bilateral salpingo-oophorectomy, had no radiation treatment, and is in good health six years after the surgery. The third case, from whom was removed a right ovarian tumor of this type, subsequently has had three pregnancies and good health during the past five years.

The author stresses the value of Föderl prognostic indications based upon the degree and type of necrobiotic changes of the tumor cells found in lymphatics to the individualization of therapy.

C. E. FOLSON.

**Kleitsman, R.: A Contribution on the Pathology and Clinical Aspects of Granulosa-Cell Tumors, Acta obst. et gynec. Scandinav. 26: 60-84, 1946.**

Kleitsman describes in detail, using six photomicrographs, five cases of granulosa cell tumor, observed during the past thirteen years at the Gynecology Clinic of the Public Maternity Hospital, Stockholm. Four cases were benign and occurred unilaterally and, according to Kleitsman, do not result in metastases or recurrences. The author feels an important clinical symptom of the benign granulosa-cell tumors is the endometrial hyperplasia, which in women *before* the menopause is linked with amenorrhea and possibly metrorrhagia, but in postmenopausal cases with irregular hemorrhages. In the benign tumors the author concludes postoperative roentgen treatment is unnecessary.

C. E. FOLSON.

**Sorba, M.: Gonadotropins and Ovarian Tumors. Gonadotropinuria in a Case of Primary Polyembryonic Dysembryoma and Chorionepithelioma with Incomplete Precocious Puberty, Gynaecologia 122: 53-67, 1946.**

Sorba reviews the extant literature of ovarian tumors exhibiting urinary gonadotrophic activity. He adds a case of a two-year-old female infant. The child, during a six-month interval, complained of intermittent abdominal discomfort, gradually developed a large abdominal mass. She was subjected to usual methods for diagnosis. It remained for exploratory laparotomy to reveal a primary right ovarian tumor (1,420 Gm.) with obvious metastasis to the right iliac and aortic lymph node chains. A similar type tumor, walnut sized, was found on the left ovary.

The first microscopic diagnosis, by J. F. Nicod, was malignant dysembryoma. Subsequent study classified the tumor as an embryonal teratoblastoma with chorionepithelioma.

The uterus and the breasts were enlarged, indicating functional activity of the tumor. The urinary gonadotropin curve was similar to that encountered in certain testicular tumor exhibiting metastases. The postoperative fall was followed by a subsequent rise, indicating further metastatic development, which later value dropped to normal values (less than 2 units per liter) just before death. Autopsy was not granted.

C. E. FOLSON.

the retroversion per se, but the concomitant edema of the endometrium that is responsible. The same author states on page 736: "Displacements of the uterus, more particularly retroflexion and prolapse, are justly considered as important factors in the causation of abortion." Stander continues on page 742: "Prophylactic treatment is most important although, as a rule, it is not available in women aborting for the first time. After the patient has recovered from an abortion, a careful local and general physical examination should be made and, in case any abnormality is discovered, the necessary curative or precautionary measures should be instituted before renewed conception occurs. If the uterus is retroflexed, the organ should be replaced and held in position by a properly fitting pessary." Curtis states in this connection (ed. 5, p. 451): "A uterus which is temporarily retrodisplaced, and enlarged and congested, such as is encountered after abortion and in the puerperium, may be satisfactorily treated with simple measures. The pessary, despite its waning popularity, finds itself of greatest usefulness in these cases."

In addition to using the pessary in certain patients with retroversion who have had repeated spontaneous abortions, other therapy is employed including hormones, vitamins, and dietary measures.

Dr. Atlee states (Canad. M. A. J. 37: 547, 1937), "A retroverted uterus can be disregarded in the postpartum examination."

3. *Nausea and Vomiting of Pregnancy.*—In Stander's Clinic, such patients are treated with intravenous glucose, sodium lactate (if necessary) and small feedings. The uterus, if retroverted, is replaced as an adjuvant to this therapy. Using such a regimen, therapeutic abortion has been unnecessary for vomiting of pregnancy since 1938 (Kuder and Finn, AM. J. OBST. & GYNEC. 49: 762, 1945). Stander states in this connection (ed. 9, p. 578), "When abnormalities of the generative tract are discovered, they should be corrected, the displaced uterus should be replaced and held in position by a properly fitting pessary."

Dr. Atlee has stated (Canad. M. A. J. 41: 750, 1934) that pernicious vomiting is always a neurotic manifestation. He reported 33 cases treated by suggestion, three of whom required therapeutic abortion.

4. *Backache.*—Curtis says (ed. 5, p. 451), "A patient with bad retroversion may suffer from backache and bearing down discomfort." The same author states on page 602, "Backache is quite often caused by retrodisplacement and is relieved by its correction."

Dr. Atlee states (Canad. M. A. J. 53: 122, 1945) that a suspension failed to relieve a patient of backache, pain, and weight in the pelvis. It is quite possible that manual replacement and a therapeutic trial with a well-fitting pessary would have given the same information.

5. *Incarcerated Uterus.*—Dr. Atlee states that he has seen an incarcerated uterus only once in 4,000 cases. At the New York Lying-In Hospital, where nearly that many patients are delivered yearly, one is in a position to see uterine incarceration more frequently. The writer has observed this complication at least 12 to 15 times on the ward service, in his own cases, or those of other attending obstetricians. Dr. Erwin Smith and the writer replaced an incarcerated uterus successfully in the past month, without anesthesia, thereby relieving the patient's symptoms.

CARL T. JAVERT, M.D.

530 EAST 70TH STREET,  
NEW YORK CITY.  
JANUARY 20, 1947.

## A Suggestion for Relief of Pain in Episiotomy Wounds

To the Editor:

A certain number of women complain of pain in the episiotomy wound as being the most uncomfortable thing in their postpartum course. The use of fine catgut, the loose tying of sutures, and the avoidance of too much catgut will do much to make the postoperative course less painful. Silkworm gut seems to cause more discomfort than other suture material. In spite of all these measures, there still exists discomfort in a considerable number.

Evidently these indications are not acceptable to Dr. Atlee, judging from his letter, as well as his statements in the literature. However, the author mentioned them because they are the accepted opinions of American authorities on the subject, and the ones which he has been taught. Inasmuch as Dr. Atlee disagrees with these accepted indications for the use of a pessary, the burden of proof is upon him. The writer agrees with Dr. Atlee that the indications may be open to question, and for that very reason, when an opportunity arose to test them, he did so in a small series of patients, under the following circumstances.

During World War II, civilian dependent care placed an added responsibility on medical officers. Facilities for hospitalization of patients with abortion, nausea, and vomiting, backache with retroversion (even those relieved by pessary), and for the study of sterility, were not available. Often one was hard put to care for these conditions in the outpatient clinic. Under such circumstances, one wished to leave no stone unturned in doing the utmost to relieve the patient's symptoms or complaints. Moreover, there was an important morale factor (the soldier husband) to be considered. The number of patients seemed too small (there were fifty-five) for a statistical breakdown into the various categories, so it was not done. The Post Surgeon concurred in making the report as a worth-while experience, and it was sent through the customary military channels for approval, which was granted.

Subsequent experience with the combined procedure has shown its value. The author has been impressed with the ease with which a pregnant uterus turns over in the knee chest position, whereas the nonpregnant organ has resisted attempts at complete correction on several occasions, and only a semireposition has been obtained.

The pessary is not used frequently enough in patients with uterine retroversion, perhaps because not every doctor knows how to replace a uterus and insert a properly fitting pessary. That may be the reason for their failure to get the expected results. Realizing this, the writer dared to hope that the use of the combined procedure (which he has seen others employ with variation for over a decade) would facilitate replacement of the uterus. By no means does the writer recommend the pessary for every case of retroversion. He stated that lack of symptoms was a contraindication to its use in nonpregnant women. Asymptomatic retroversion is perhaps as common as symptomatic displacement.

Dr. Atlee's letter also makes reference to the article in connection with the "atrocious number of useless suspensions being done at present" and fears that the printed word as quoted from the writer's article will mislead his students. The writer agrees with Dr. Atlee that perhaps many suspensions are done needlessly. However, the article in question makes no mention of the "accepted indications" in terms of the suspension operation. The writer does wish to state that if these indications exist, and the pessary has provided a satisfactory therapeutic test, that a suspension operation should be given consideration in the treatment of selected patients.

There is certainly no harm in permitting students to learn of the medical opinions of others, even if they are contrary to the opinions of local authority. The writer encourages students to obtain opposite points of view. Didactic teaching has no place in clinical obstetrics and gynecology. All too often does time prove such teaching to be in error. The opposition of members of the profession to the contagiousness of childbed fever and anesthetic are examples. The writer believes in the saying attributed to Voltaire, that he may disagree with what has been said but will defend unto death the right to say it.

I will try to discuss these "acceptable indications" in greater detail.

1. *Sterility*.—Dr. William H. Cary, an outstanding American authority, states in a personal communication that he corrects a retroversion if it is present and inserts a pessary. Collectively, we have seen pregnancy follow such a simple procedure in approximately twelve patients, one of which occurred in the past month. Cary is of the opinion that the cervix is best exposed to the seminal pool if the uterus is erect, thereby facilitating spermigration. Dr. Atlee reports (*Canad. M. A. J.* 53: 122, 1945) a suspension operation on a sterility patient. He does not state whether a preliminary trial had been given the pessary.

2. *Spontaneous Abortion*.—Dr. H. J. Stander states in his textbook (*Vol. 2, p. 670*): "Abortion is common in pregnancies complicated by retrodisplacements." It may not be

Round table discussions from 4 P.M. to 5 P.M. daily will consider such topics as etiology of abortion, asphyxia, fibroids, prolonged labor, infertility, early ambulation, adolescence, treatment of abortion, genital relaxation, ovulation, the menopause, the cystic ovary, uterine bleeding, nutrition in pregnancy, geriatric gynecology, endometriosis, and erythroblastosis.

Concurrent sessions and round tables for nurses, hospital administrators, and public health workers are being arranged.

The popular forceps and breech demonstrations that attracted so much attention at the Second Congress in 1942 will be increased in number so that eighteen demonstrations per day will be held, six each at 9:00, 1:00, and 5:00 o'clock daily.

A large Scientific and Educational Exhibit is being set up under the direction of Dr. J. P. Pratt of Detroit and a comprehensive Motion Picture Program is being arranged by Dr. John Parks of Washington, D. C. The committees assisting these doctors will review applications by prospective participants late this spring. Anyone wishing to make application for space in the Scientific Exhibit or for time on the Motion Picture Program may obtain the proper blanks from the office of the Congress at 24 West Ohio Street, Chicago 10, Illinois.

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### International Congress of Obstetrics and Gynecology Dublin, Ireland, July 7 to 12, 1947

The program for the Congress includes seven sessions to be devoted on successive days to the following topics: history of midwifery, puerperal sepsis, eclampsia, sterility, fetal and neonatal mortality, and shock in obstetrics. Representative speakers from several countries will discuss these topics, including the British Isles, New Zealand, the United States, Australia, South Africa, Sweden, Palestine, Denmark, Canada, and elsewhere.

Information about travel routes, hotel accommodations, etc., may be obtained from the local offices of Messrs. Thos. Cook and Sons.



A solution of equal parts of Tr. Merthiolate and 2 per cent Nupercaine solution sprayed on the episiotomy wound was found to be effective in alleviating discomfort for two to three hours. It may be repeated as necessary.

In these days of shortage of nurses, etc., there are times when optimum perineal care may not be given. The use of this spray would thus serve a twofold purpose.

MILTON M. ROZAN, M.D.

LANSING, MICHIGAN

FEBRUARY 7, 1947

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## Items

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### American Board of Obstetrics and Gynecology, Inc.

#### Examinations

The next oral examination and annual meeting of the American Board of Obstetrics and Gynecology, Inc., will be held at the Hotel William Penn, Pittsburgh, Pa., June 1 to 7, inclusive.

The following associate examiners have been appointed to assist the Directors of the Board: Dr. W. C. Danforth, 636 Church St., Evanston, Ill.; Dr. John L. Parks, Gallinger Municipal Hospital, Washington, D. C.; Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland, Ohio; Dr. S. A. Cosgrove, 88 Clifton Place, Jersey City, N. J.; Dr. L. M. Randall, Mayo Clinic, Rochester, Minn.; Dr. Nicholson J. Eastman, Johns Hopkins Hospital, Baltimore, Md.; Dr. Conrad G. Collins, Tulane University, 1430 Tulane Ave., New Orleans, La.; Dr. William J. Dieckmann, 5841 Maryland Ave., Chicago, Ill.; Dr. C. B. Lull, 807 Spruce St., Philadelphia, Pa.; Dr. J. R. Eisaman, 121 University Place, Pittsburgh, Pa.; Dr. Herbert E. Schmitz, 25 E. Washington St., Chicago, Ill.; Dr. Edward A. Schumann, M.D., Philadelphia, Pa.; Dr. Ward F. Seeley, M.D., Detroit, Mich.

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The following physicians are to be included in the list of diplomates certified by the American Board of Obstetrics and Gynecology: Dr. Earle Milliard Marsh, 17 William Street, Rockville, Md.; Dr. Kenneth Anthony O'Connor, 109 Euclid Place, Oak Ridge, Tenn.

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### Third American Congress of Obstetrics and Gynecology

The program of the Third American Congress on Obstetrics and Gynecology to be held September 8 to 12, 1947, in St. Louis will feature general sessions for all groups making up the Congress, as well as smaller individual group meetings and round table discussions. The morning sessions will be panel-type presentations of the following subjects: Tuesday, Sept. 9: Anesthesia and Analgesia; Wednesday, Sept. 10: Cancer; and Thursday, Sept. 11: Cesarean Section.

The afternoon meetings of the medical section of the Congress will consider on Tuesday: Psychosomatic Aspects of Pregnancy; on Wednesday: Pregnancy Complications; Cardiac Disease, Diabetes and Tuberculosis; and on Thursday: Recent Advances in Endocrinology.

Herkel, and Hill<sup>1</sup> pertain to the total blood flow through the whole organ of litter-bearing animals. Such determinations neglect the fact that the uterine tissues about the distended spheroidal conceptuses during the middle period of pregnancy (in litter-bearing animals) are subjected to ever-increasing tension resulting from continued growth of the conceptus. On the other hand, those parts of the uterus lying between the implantation sites are subjected to less tension. This favors a channeling of blood through such areas in preference to those parts that are under greater local tension. Blood flow measurements for the entire organ fail to reflect such local differences in the circulation. It was for this reason that a special study was initiated. This has been reported in detail in a physiologic journal (Reynolds<sup>2</sup>). Consequently, only the essential conclusions of that study need be repeated here.

In approaching the problem of differential circulation rates within the uterus, it was essential to have a method which was highly localized. It mattered little that blood flow rates in metric or any other units were not obtained. Relative rates of flow were important. The method adopted possessed these characteristics, yielding a measure of blood flow through small vascular beds. This was accomplished by injection of small volumes of sodium cyanide into the venous system of the uterus and elsewhere, and measuring the time required for the cyanide to be carried from the site of injection by blood from anastomosing vessels into the systemic circulation and to the carotid body of the mother. Calculation of the reciprocal of the circulation time yields a coefficient of the rate of blood flow. Employing this technique, blood flow rates have been compared in different parts of the vascular tree at selected times in pregnancy. In the uterus, injection was made into the lateral uterine vein in any of several locations. These were: at the site of maximum distention of the uterus about a conceptus; at interimplantation sites; in the lateral uterine veins of nongravid uteri of unilaterally sterilized rabbits. In addition, circulation times were measured from the femoral vein to the carotid body, in order to evaluate the blood flow rate in the systemic circulation of the mother.

The essential features of the local circulation of maternal blood in pregnant rabbits is shown in curve A of Fig. 1. Here, blood flow rates at different periods of pregnancy are shown as a percentage of the pre-pregnancy blood flow rate. It will be seen that there is a gradual and progressive decrease until the twentieth day, to 68 per cent of the pre-pregnancy level. Upon attainment of maximum spheroidal size (about the twenty-second day) there is a profound and sudden decrease in circulation rate to a quarter of the pre-pregnancy level. Clearly, a critical condition develops with respect to the local uterine circulation about the conceptus at the beginning of the last trimester of gestation in the rabbit. The condition does not last for long, however. At this point, the conceptus undergoes elongation, and with this, there is an immediate restoration of the local blood flow to a relatively high level. It is 75 per cent of the pre-pregnancy circulation rate, or about equal to that which is found on the twelfth day of pregnancy, early in the period of spherical growth of the conceptus.

The situation described for the local circulation about the conceptus is not paralleled by that in any of the other parts of the vascular tree for which blood

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## Original Communications

### UTERINE ACCOMMODATION OF THE PRODUCTS OF CONCEPTION: PHYSIOLOGIC CONSIDERATIONS

S. R. M. REYNOLDS, PH.D., BALTIMORE, MD.

(From the Department of Embryology, Carnegie Institution of Washington)

THE size and shape of the gravid uterus is a necessary and primary subject of interest to the obstetrician. So axiomatic is this fact that little thought is given generally to its implications. When it is given consideration, it is usually with respect to the morphology of the uterus, or to the size of the conceptus with respect to the estimated age of pregnancy. One seldom thinks that this phase of obstetrics offers a broad field for fruitful investigation. The recent paper by Ivy<sup>6</sup> shows that our knowledge is not yet complete with regard to the extent to which the *isthmus uteri* contributes to the uterine wall about the conceptus in the latter part of pregnancy. More recent studies made on infra-primate species suggest that still other attributes of uterine accommodation of the products of conception will bear the attention of clinician and experimenter alike, for these pertain to important physiologic mechanisms that are concerned with fetal growth and welfare. The new data have already yielded conclusions which promise to provide a common basis upon which certain of the functional, and seemingly unrelated, difficulties of late pregnancy may be explained. Uterine accommodation of the products of conception appears to be the common physiologic denominator to these situations. The functional components of uterine accommodation include, (1) the hemodynamic conditions of the flow of maternal blood in the uterine wall; (2) the hydrostatic relations involved; (3) the problem of uterine growth; (4) the extent to which the observations thus far made apply to other species and to other types of uteri; and finally, (5) the relation of the foregoing considerations to fetal growth and to fetal and maternal welfare.

#### Uterine Circulation and the Shape of the Conceptus

Despite its obvious importance, the question of maternal blood flow through the uterus has been little studied (cf. Reynolds<sup>5</sup>). Observations by Barcroft,

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

There is more direct evidence that the shape, and not mere distention, plays a determining role in affecting the maternal blood flow locally. This was obtained when observations were made upon three uteri on the twenty-second day of gestation. Some of the fetuses had undergone elongation. Others were still in the spherical state (see Fig. 2). The blood flow rates were measured in each type of conceptus. The effective head of arterial blood pressure and the place in the vascular tree was comparable for each type of conceptus site. In spite of this, the blood flow rate through the spherically distended uterus was exceedingly slow, whereas at the elongated conceptus sites, the circulation rate was at a significantly higher level (Reynolds<sup>9</sup>). The conclusion therefore follows that the shape of the distending conceptus is the principal local determiner of the efficiency of the local vascular system. The physical nature of these local conditions, particularly of shape, has been a subject of a separate study (Reynolds<sup>10</sup>). The argument resolves itself into a general discussion of the hydrostatic forces involved in hollow elastic bodies as described by Hess<sup>4</sup> for the cardiovascular system and as shown to be generally applicable to hollow viscera by Sutherland.<sup>15</sup>

### Hydrostatic Conditions and Shape of the Conceptus

When the uterus is distended by a spheroidal conceptus, it is forced into a position which imposes, for any unit of surface, a degree of tension *which is a function of the product of the respective radii*. In the simplest situation of a perfect sphere, the relation is expressed by the following equation:  $T_s = \frac{r^2 \cdot p}{2}$  where  $T_s$  is the tension;  $r$ , the radius; and  $p$ , the pressure within the sphere. A moment of reflection will show that even though intrauterine pressure may change but little, the mere fact that the radius of the spheroids increases about 100 per cent between the twelfth and the twenty-second day of gestation in the rabbit, the tension in the uterine wall increases *as a function of the square of this value*. Tissue tension, it has been suggested (Reynolds<sup>9</sup>), offers a pattern of increasing resistance to the entry of blood from the uterine arteries in the broad ligament into the small vessels within the wall of the uterus.

What is the situation in the wall of a hollow elastic cylinder? Simply stated, the tension in the wall is less than it is in the wall of a spheroid of equal radius and pressure. Moreover, there are two tension components, not one as in the sphere. In a circular direction, the tension is a function of the product of the radius and the pressure ( $T_c = r \cdot p$ ). In a longitudinal direction, it is one half this ( $T_l = \frac{r \cdot p}{2}$ ).

The process of elongation of the uterus may be regarded, therefore, as a mechanism which serves to relieve the hydrostatic tension on the uterine wall, thus permitting restoration of the flow of maternal blood in the uterus about the conceptus. At the same time, this change permits rapid enlargement of the fetus during the last trimester of pregnancy with minimal increase in average uterine wall tension, at least until near term. Consequently, the pattern of ten-

flow rates have been determined. The circulation rate in nongravid cornua of unilateral pregnancies in rabbits shows no change before the twenty-eighth day. The systemic circulation rate, as judged by femoral-carotid circulation times, diminishes slightly but significantly during the first half of gestation. It then increases to a maximum on the twenty-second day at the time of greatest difficulty with respect to the uterine circulation about the conceptuses. The increase in systemic circulation rate—which may be a compensatory homeostatic response on the part of the maternal organism—is inadequate to overcome the critical local condition which attainment of maximal spheroidal size brings about in the uterus. What conditions, one asks, govern the local circulatory efficiency of maternal blood flow in the uterus?

### Change in Shape of the Conceptus During Pregnancy

In Fig. 1, curve *B*, the relative shapes and sizes of the conceptus sites in the gravid uterus are shown for certain periods of pregnancy. Several interesting features of these changes should be noted in order to appreciate the local circulatory conditions outlined above.

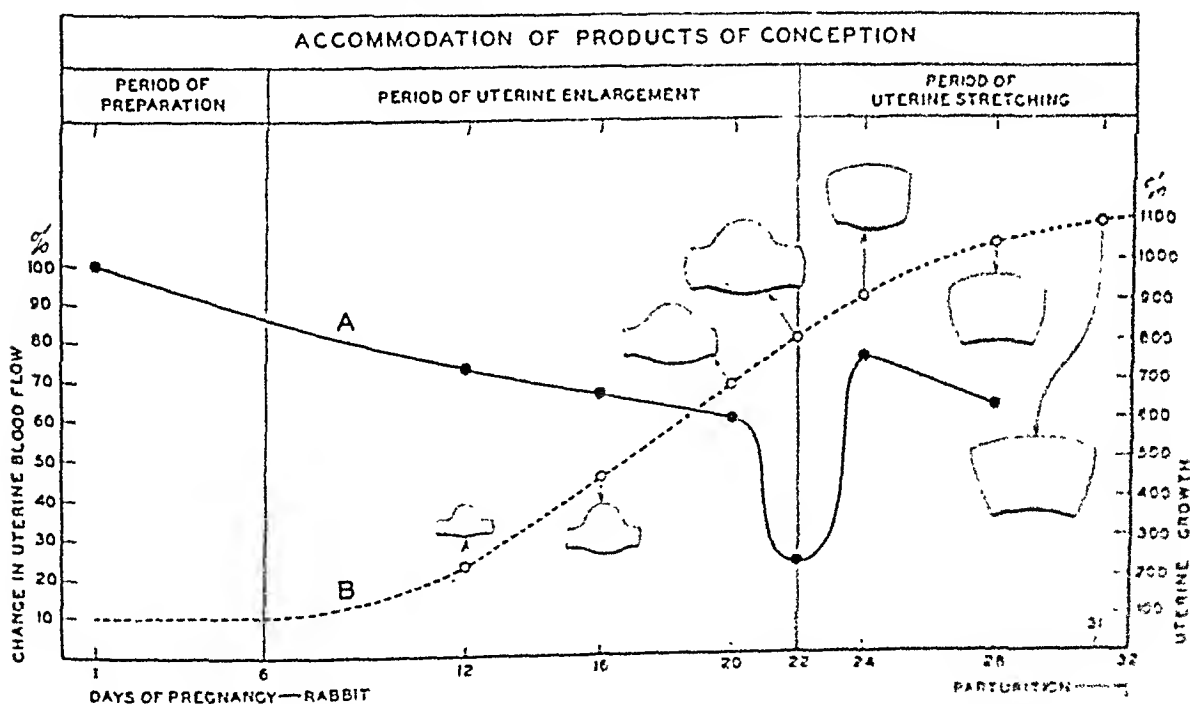


Fig. 1.—Uterine accommodation of the conceptus in the rabbit. Curve *A*, local blood flow through the lateral uterine vein in the uterine wall. Curve *B*, increase in weight of the uterus during pregnancy, showing the relative size and shape of the conceptus at different times. See text for discussion of the significance of conversion of the conceptus from spheroidal to cylindrical shape.

First, throughout the period when the conceptus possesses a spherical shape, the circulation rate of maternal blood through the uterus decreases. Second, the blood flow diminishes as the size of the spheroid conceptus increases. Third, after the spheroid loses its spherical shape, the circulation of maternal blood about the conceptus is restored to a comparatively high level. Clearly, this elongation of the conceptus after temporary embarrassment of the local circulation is associated with relief of resistance to the flow of maternal blood through the greatly distended uterus.

Soon after implantation, uterine distention begins as a result of the growth of the trophoblast and its associated structures, and from distention from the accumulation of fluid within the conceptus. Distention in a spheroidal shape creates, as we have seen, the maximum local tension within the uterine wall. It is interesting to observe in this connection that *tension* is one of the most effective stimuli favoring uterine growth (Reynolds,<sup>7, 8</sup> Reynolds and Kaminester<sup>12</sup>). The role of tension as a stimulus of uterine growth is demonstrated by two types of observation. First, when one uterus of a rabbit is rendered sterile by prior ligation of the Fallopian tube, that nongravid uterus does not increase in size appreciably throughout the first two-thirds of pregnancy in the opposite uterus. The nongravid uterus lacks the stimulus of distention, although its hormonal supply is similar to that of the contralateral growing and distended uterus. Second, distention of the uterus of untreated castrated rabbits evokes a uterine growth response (Reynolds and Kaminester<sup>12</sup>). Thus, we see, the spheroidal conceptus in pregnancy may elicit its own growth of the uterus through local distention, and for this the conceptus possesses a most effective shape.

The last third of pregnancy brings about a new situation. With elongation of the conceptus, the rate of growth of the uterus becomes much less and there is, at the same time, as we have seen, a marked decrease in the tension to which the uterine wall is subjected. It is at just this time that full flow of maternal blood to the uterus is re-established and the fetus commences to grow most rapidly. This correlation with fetal growth is shown by data pertaining to the size of the fetal rabbit (Hammond<sup>3</sup>). Under rigid conditions designed to minimize genetic and random influences, the weight of rabbit fetuses at selected periods of pregnancy was determined as follows:

Sixteenth day of pregnancy	0.58 Gm.
Twentieth day of pregnancy	2.96 Gm.
Twenty-fourth day of pregnancy	13.42 Gm.
Birth (thirty-second day of pregnancy)	70.00 Gm.

Here, it will be observed, there is marked fetal growth at a time when the uterus is no longer enlarging appreciably. It is therefore evident that the last trimester of pregnancy in the rabbit is a period of uterine stretching. This consists of a "paying out" of tissue elements which are laid down by pregestational proliferation during a period of preparation of the uterus in the earliest part of pregnancy and which increase in size by hypertrophy during the period of most rapid uterine growth.

It is worth emphasizing again that stretching of the uterus in the last trimester is accomplished under circumstances which impose least tension upon the uterine tissues, and which interfere least with the local circulation of blood to the conceptus. In this way, there is a nice integration of structural and functional factors which operate throughout the entire period of gestation. Taken together, these provide the mechanism of uterine accommodation of the products of conception. The key to this mechanism is found to be the *shape* of the products of conception although other factors relating to hormonal conditions,

sion within the uterine wall is governed largely by the shape and size of its contents. The relation of this pattern of tissue tension to the local flow of blood within the uterine wall is discussed in the previous section, above. There is reason to believe that this relation may bear a causal relation to other aspects of uterine function as well, especially in so far as the growth of uterine tissues in pregnancy is concerned. This has been reviewed in a previous publication (Reynolds<sup>10</sup>) so the results of that study may be summarized briefly.

### Uterine Growth and the Shape of the Conceptus

The curve of uterine enlargement during pregnancy in the rabbit is shown in Curve *B* of Fig. 1. The shape of this curve is characteristic of growth curves in general in that it is sigmoid. Clearly, the stimulus for uterine enlargement does not exist until after the first week of gestation in the rabbit; it then continues effectively throughout the entire period during which the conceptuses are spheroidal. The stimulus diminishes as soon as the conceptuses merge, or grow sufficiently to form cylinders.

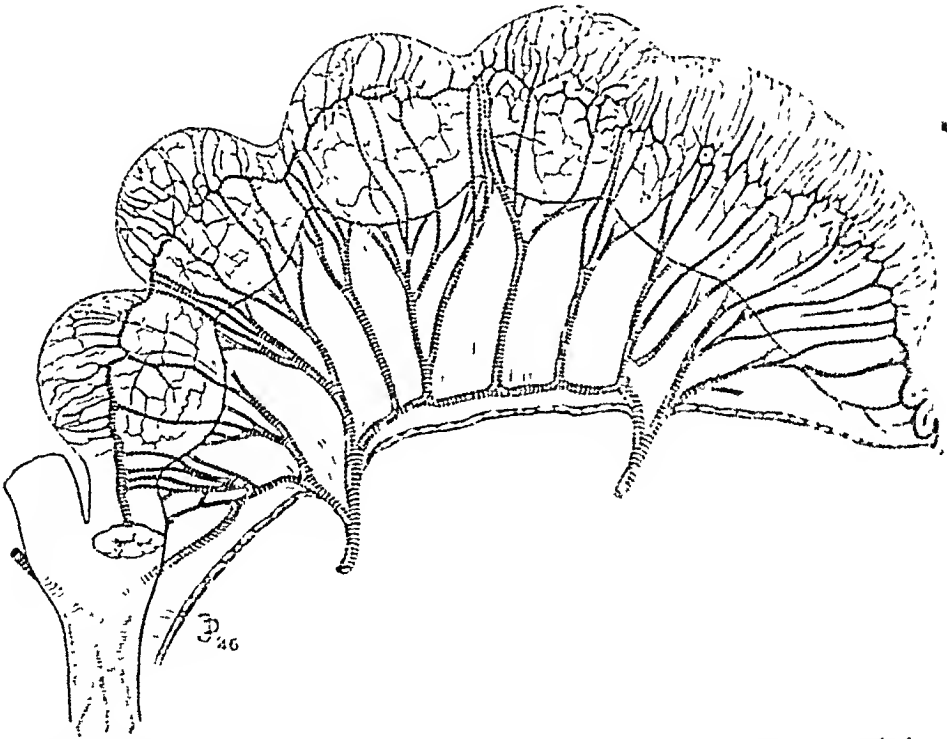


Fig. 2.—Drawing of a freshly fixed uterus of a rabbit on the twenty-second day of pregnancy (two-thirds of the duration of pregnancy) in the process of conversion of the conceptus from spheres to cylinders. See text for discussion of the results of the measurement of blood flow through the uterus about the two types of conceptus shown, and with respect to rearrangement of the vascular architecture. Drawn by Mr. James F. Dblusch.

The nature of the growth factors which operate at this time have been reviewed (Reynolds<sup>7, 8, 10</sup>). In brief, the initial period of the uterine growth curve, before extensive enlargement, is a period of hyperplasia both of endometrial elements and of myometrial elements (pregestational proliferation). It is characterized, accordingly, by an increase in the number of cellular units which are available for subsequent hypertrophy as well as by preparation of the endometrium for implantation of the blastocysts.

spheroidal conceptuses (the second from the cervix was used) was extremely sluggish. The circulation rate through the elongated cylindrical conceptuses was rapid, however.

It is believed that the process of conversion from spheroid to cylinder is very rapid. The basis for this belief lies in the fact that all the conceptuses in a uterus usually are of one type or of the other. Only rarely is the situation shown in Fig. 2 seen. It follows, accordingly, that when the situation becomes critical with respect to the local flow of maternal blood, a rapid readjustment is usually made. If it were not, then the welfare of the fetus might be jeopardized. Evidence has been adduced elsewhere to show that in the rabbit the onset of the incidence of fetal death (determined by gross fetal resorption) in late pregnancy coincides with this period of conversion of the conceptus from spheroid to cylinder.

So much for the structural and functional factors involved in the mechanism of uterine accommodation of the products of conception. What has been said pertains to the rabbit which has a uterus duplex. Is there any evidence that these special conditions have a counterpart in other species possessing a *uterus duplex*, and in those having a *uterus bicornis* and a *uterus simplex*?

### Comparative Aspects of the Mechanism of Uterine Accommodation

Since direct observations pertaining to uterine accommodation have been made solely in the rabbit, there is indirect evidence only that they have a counterpart in other species. We must rely upon a few scattered data pertaining to the form of the uterine growth curve and to the dimensions and thickness of the uterus at different periods of pregnancy. Even so, there is telling proof that what has been described in some detail for the rabbit is true also for other species with similar and with other forms of uteri. There are differences in some with respect to the time of conversion and in others in the pattern of conversion. But so far as existing data go, there is no known exception to the general principle that accommodation of the products of conception by the uterus is locally controlled by the shape of the conceptus.

*Uterus duplex*.—The curve of uterine growth in the rat appears to have been determined first by Siegmund<sup>13</sup> (summarized in Reynolds<sup>8</sup>). It was found that the growth curve is sigmoid, as in the rabbit, with the stimulus for rapid uterine growth awaiting implantation of the blastocysts. The point of diminishing uterine growth comparable to that in the rabbit takes place about the eighteenth day of pregnancy. This is only three days before parturition in this species. The inflection in the uterine growth curve in the rat is coincident with conversion from spheroid to cylindrical shape of the conceptus (unpublished data of Dr. Philip Rogers, personal communication, and L. T. Bradin, personal communication). Except, therefore, for the shorter proportion of pregnancy during which the fetuses are in the cylindrically shaped uterus, the situation appears to be entirely comparable to that which has been observed in the rabbit. This constitutes the extent of detailed information of the growth and conversion of the uterus duplex in the latter part of pregnancy, with the exception of several observations which have been made on the golden hamster in this laboratory. In this species pregnancy lasts but sixteen days. The conceptuses have been seen to be spheroidal on the fifteenth day. Conversion would seem to be closely asso-



to the size of the conceptus, and so forth, contribute to the effect which change in shape of the conceptus will have upon the uterus.

### Shape of the Conceptus and Rearrangement of the Uterine Blood Vessels

The fact that change in shape and increase in size of the conceptus affects the circulation of blood locally through changes in tension on the uterine wall suggests that an investigation of the re-orientation of the vascular bed during gestation should prove fruitful. Such a study has been started, and will be reported separately elsewhere. Enough has been learned, however, to indicate the essential features of this adjustment.

The methods of studying this were twofold. First, diffusible salts (potassium ferrocyanide and iron ammonium citrate) were injected caudally below the renal artery into the aorta under a pressure of 110 millimeters of mercury. The excised uterus was then immersed in acid, and the tissues became colored by deposition of Prussian blue wherever the salts had penetrated the tissues. This, of course, was governed by the patency of the vessels at the time of injection. Second, injection-corrosion preparations were made of the uterus after injection of vinylacetate into the blood vessels. Red was used for arteries and blue for veins. After digesting away the soft tissues, the pattern of the larger blood vessels of the uterus could be seen readily. This method was used in the injection of the spiral artery recently reported to be in the hilus of the ovary (Reynolds<sup>11</sup>).

The injection of diffusible dye shows that it is distributed uniformly throughout the uterus, both about the conceptuses and between them, through the sixteenth day of pregnancy. By the twentieth day, however, the regions about the conceptuses are paler than the adjacent areas. By the twenty-second day, the dye is virtually absent from the region of distention *if the conceptus is spheroidal*. In those instances in which conversion to the elongated or cylindrical form has taken place by the twenty-second day, the dye is found in increasing concentration in the uterine tissues over the conceptus. These data parallel the circulation-rate data summarized above. Taken together, they comprise physiologic and morphologic evidence of the effect of hydrostatic forces upon the patency of the small blood vessels of the uterus.

The vascular tree in the injection-corrosion preparations shows in a different manner the effect of hydrostatic forces upon the vascular architecture in the uterine wall about the conceptus sites. For example, in addition to an increase in size of all of these vessels, there are profound alterations in their distribution. It was found that an increase in spheroidal size of the conceptus serves to force the larger blood vessels within the uterine wall to each end of the conceptus, with resulting extension of the remaining blood vessels within the wall of the uterus. Conversion of the sphere to an elongated cylinder, however, permits a re-grouping of the blood vessels which have been forced to the inter-implantation sites, so that they become more evenly spaced along the lateral wall of the cylinder. This is shown in a drawing (Fig. 2) which was made of a freshly fixed specimen obtained on the twenty-second day of pregnancy. This rabbit had been used for circulation rate studies. The blood flow through the veins of the

ciated with parturition in this form. If so, it may be more than a coincidence that the newborn hamster which is in the elongating uterus for less than one-fifteenth of the duration of pregnancy is born in an exceedingly immature state of development. The rat, which remains in the elongating uterus for about one-seventh of pregnancy, is more developed at birth than the hamster, whereas the rabbit, which spends one-third of its fetal life in the elongating uterus, is still more advanced than the rat in its development at birth. Markedly post-mature fetuses are obtained in both rabbits (Snyder<sup>14</sup>) and rats (Hooper<sup>5</sup>) if pregnancy is prolonged experimentally by several days. Perhaps the statement may be made, when more is known regarding this suggested relationship, that *fetal maturity at birth depends upon the proportion of pregnancy which the fetus spends under the optimal conditions for fetal growth in the elongating uterus.*

*Uterus Bicornis.*—We have little information on the curve of uterine growth in any species having this type of uterus. The only data known to this writer are those of Hammond<sup>2</sup> for the cow (cf. Reynolds<sup>8</sup>). These data show that the uterus exhibits a sigmoid growth curve. Noticeable uterine enlargement begins about the second month of pregnancy, and continues at an accelerating rate until about the seventh month. After this, there is, as in the case of the other species discussed above, a period in which little further increase in size of the uterus takes place. Nevertheless, the fetus increases in size from about thirteen or fourteen kilograms to twenty-six or twenty-seven kilograms during the last two months of pregnancy.

*Uterus Simplex.*—The data which are available for the purposes of the present discussion with respect to this type of uterus are exceedingly limited. Dr. Elizabeth M. Ramsey has made available for study four monkey uteri obtained at very carefully selected periods of pregnancy. Data from the human being have been secured from the measurements cited by Ivy,<sup>6</sup> and from the section by Prof. Rosthorn in v. Winckels' *Handbuch der Geburtshilfe*.<sup>16</sup> In addition, reference has been made to limited materials suitable for such a study which are available in the Carnegie Embryological Collection. On the basis of these studies, the relations shown in Fig. 3 have been tentatively established.

In Fig. 3a, the outlines of the *transverse sections* of the monkey uterus at the point of maximum measurement are shown in a scale of one-eighth size, and the similar outlines are shown for the human uterus in a scale of one-sixteenth size. For comparison, similar outlines are shown for the rabbit uterus drawn to a scale of one-fourth size. All are shown at their respective periods of gestation, expressing the total duration of pregnancy in each as 100 per cent.

In compiling these data, several striking relationships were apparent at once. In the first place, the rabbit and the monkey possess a common pattern in the development of the transverse outline of the pregnant uterus. During the first two-thirds of gestation, there is an increase in transverse and dorsoventral diameters alike. In the last third of pregnancy, the increase in either of these diameters is very small, at least until just before term. The condition in the human was observed to be quite different and this difference was consistently noted regardless of which source of material was consulted. Up to the last third of gestation (in the sixth lunar month) there is a progressive increase in dorsoventral and lateral diameters, as in the rabbit, and monkey. After the sixth month the lateral dimension of the uterus continues to increase while the dorsoventral diameter changes relatively little until just before term. Clearly,

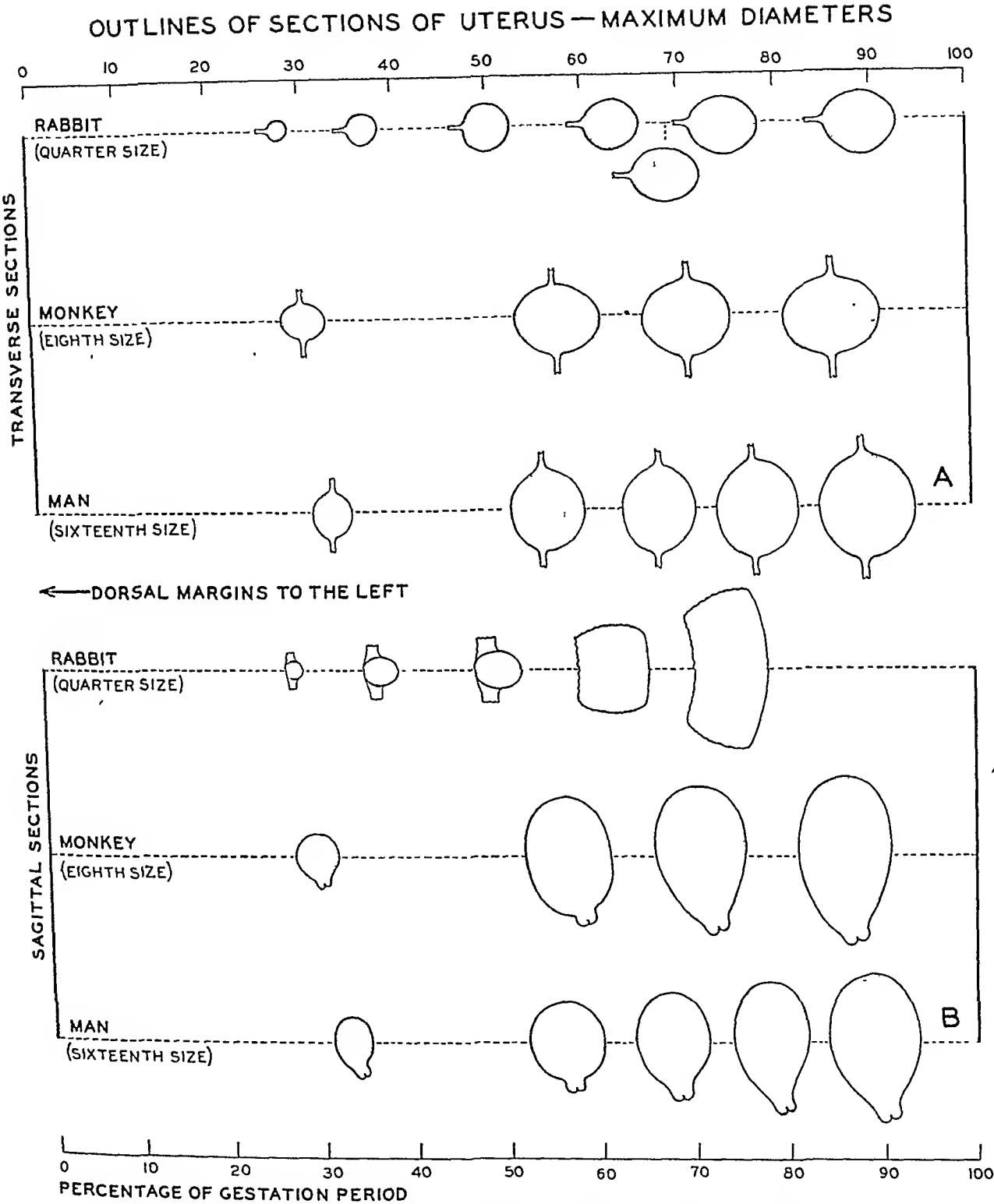


Fig. 3.—Comparison of transverse (top) and sagittal (bottom) outlines of the uteri of the rabbit, monkey, and human being (at different periods of pregnancy). Drawn to a scale of 1,  $\frac{1}{4}$  and  $\frac{1}{8}$  for rabbit, monkey, and human being respectively. Dorsal aspect of uterus to the left, ventral to the right. Note three-dimensional growth of the conceptus through the first two-thirds of pregnancy. In the last trimester, growth of the conceptus during "elongation" is uni-dimensional in the rabbit and monkey, but bi-dimensional in the human. See text for discussion of the significance of no appreciable change in the dorsoventral measurement of all three in the last third of pregnancy in maintaining a nearly fixed curvature to the lateral margins of the uterus.

the others. It may be that in the uterus simplex the situation is more complicated. Uterine ischemia of given degree or duration may bring harm to the maternal organism by giving rise to toxic manifestations, or it may give rise to local conditions which jeopardize the continuance of pregnancy or the viability of the fetus.

### Summary

1. This paper offers a general discussion of the physiologic mechanisms of uterine accommodation of the products of conception. It summarizes recent experimental and basic considerations of the subject published in other journals with respect to infra-primate species, and it includes reference to the readjustments that take place in the arrangement of the blood vessels of the uterus. The features of uterine accommodation discussed are:

(1) *Uterine circulation*. It is shown that the local circulation of maternal blood in the uterus decreases gradually as the conceptus increases in size. Suddenly, as the conceptus reaches maximum ovoid size, a profound transitory decrease in uterine circulation (i.e., uterine ischemia) takes place. The conceptus changes shape abruptly (by elongation) and with this, there is restoration of a rapid circulation of maternal blood through the uterus. (2) *Hydrostatic forces in the uterus*. It is shown that the existence of an ovoid shape with respect to the conceptus imparts a relatively high degree of tension about the conceptus, even though intrauterine pressure is relatively low. The radii increase rapidly in three dimensions at this time and local tissue tension increases in *geometric* proportion. With elongation, there is an abrupt decrease in tissue tension, so that further increase in size of the conceptus evokes an increase in local tension in *linear* rather than geometric proportion. (3) *Uterine growth*. In pregnancy, hypertrophy of uterine tissues is associated with uterine distention by an ovoid conceptus. Consequently, it takes place at the time of maximum uterine tension. After elongation of the products of conception, uterine growth decreases sharply, and at this time there is the least possible increment in uterine tension with fetal growth. The last trimester of pregnancy (when fetal growth is most rapid) consists of "paying out" tissue elements which increase first by hyperplasia and then undergo hypertrophy in earlier periods of pregnancy. (4) *Vascular architecture of the uterus*. This is shown to change in such a way that the uterine ischemia which develops, with its ensuing relief, follows a pattern which may be explained on the basis of the local hydrostatic forces noted above. (5) *Comparative aspects of uterine accommodation* are discussed. This is a subject necessitating extensive study. Nevertheless, there is reason to believe that the *uterus duplex*, the *uterus bicornis*, and the *uterus simplex* all manifest the various essential characteristics of uterine accommodation described in this paper. The situation in the monkey more nearly resembles that in the rabbit than it does that in the human being. All three, however, have in common the fact that during the phase of principal elongation of the uterus, conditions are such that local tension of the tissues about the region of entry and exit of the uterine blood vessels is held to the lowest possible level compatible with rapid enlargement of the fetus. (6) Since

the condition is not like that found in the rabbit and in the monkey. We shall return to this point later in discussing the significance of these different relationships.

In Fig. 3b, the sagittal outline of the uterus of the rabbit, the monkey, and the human being are shown in the same proportions as in Fig. 3a for different periods of pregnancy. It will be seen that there is elongation of the uterus in every case, particularly during the last trimester of gestation. Thus the period of elongation, in contrast to the period of growth in all dimensions, is characteristic for the three species, with the added fact that in the human being there is growth in the lateral dimension during this period also. Of what significance is it that in the rabbit and monkey there is no important change in any of the transverse measurements of the uterus during the last period of elongation, whereas in the human only the dorsoventral diameter remains relatively constant?

The answer to the foregoing question is not known. It may be argued with reason, however, that in one very fundamental respect there is a point of similarity between the three types of uteri shown in Fig. 3. It is that there is a relationship between the tension within the uterine tissues and the radius of curvature of the uterus, as pointed out in a previous section above. In the human, the dorsoventral dimension does not increase perceptibly during the period of uterine stretching, with the result that elongation in this uterus involves a two-dimensional change with preservation of the curvature of the lateral margin of the uterus. In the monkey and the rabbit, elongation of the products of conception is unidimensional, so that here, too, the radius of curvature of the lateral margin of the uterus is preserved during this period with little or no alteration. Inasmuch, then, as the radius of curvature of the lateral margins of the uterus does not change perceptibly during the period of uterine elongation in any of the three kinds of uteri considered, *this is the essential structural feature in common between these three types of uteri during the period of uterine stretching.* This part of the uterus is the region of entry and of exit of the large blood vessels of the uterus in each of the types of uteri discussed. It is this region, accordingly, which is subjected to least stress with rapid fetal growth after conversion of the conceptus from spheroid to something approximating cylindrical shape.

### **Uterine Accommodation and Maternal and Fetal Welfare**

Attention of investigators may be directed with profit in the future to the characteristics of a proper conversion of the human uterus from ovoid to cylindrical (or pyriform) shape at the beginning of the last trimester of pregnancy. Certainly there are good experimental grounds for suspecting that unusually prolonged or unusually profound ischemia of the maternal circulation in the uterus at this time could produce changes which are either detrimental to, or totally destructive of, the fetus. In the rabbit a relationship has been pointed out already between the incidence of fetal resorption (Reynolds<sup>10</sup> and conversion of the uterus at the beginning of the last third of gestation. In this litter-bearing animal, each conceptus normally survives or dies independently of

## THE PROBLEM OF THE REPEAT CESAREAN SECTION— A PRELIMINARY STUDY

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A PRECISE knowledge of the maternal risk in repeated sections is lacking. True, there is no scarcity of opinions, but generally these are mere statements of personal beliefs, or, when supported by evidence, the experience on close examination hardly warrants the broad conclusions drawn. That there is a cumulative risk in repeat sections is believed by Adair,<sup>1, 2</sup> Gordon and Rosenthal,<sup>3</sup> Hawks,<sup>4</sup> DeLee,<sup>5</sup> and Orengo<sup>6</sup>. Sometimes contrary opinions are expressed. Thus Bride,<sup>7</sup> Arnott,<sup>8</sup> Barrett,<sup>9</sup> and Berkeley<sup>10</sup> believe that there is no increased risk. Recently Dieckmann and Daily<sup>11</sup> remarked: "Most statistics indicate that the elective repeat cesarean section has a lower mortality than that of the primary operation." This is generally true if one compares the elective repeat low section with the primary operation where cases in labor are included. But comparisons of elective repeat with elective primary for disproportion reveal that the former has a much higher mortality. Thus, in the preparation of Table I, 7,106 cesareans (the total of both primary and repeat) showed a mortality of 2.9 per cent as compared with 3.2 per cent for the repeat sections alone. An attempt to arrive at a true knowledge of the risk of repeat section should involve a detailed study of individual experiences large enough to reduce the element of chance in statistical reports to a negligible quantity. Mass statistics are not only undependable, but frequently downright misleading. Bourne<sup>12</sup> and Schumann<sup>13</sup> stress the weakness of mass statistics and surveys. But the true Achilles' heel of these mass surveys is not always a prejudiced or hasty or careless interpretation, but is often, and in fact usually, the large number of scanty, unintelligent, and sometimes evasive case histories, incomplete from so many viewpoints that they are quite inadequate material on which to base a proper interpretation. The mere quotation of mass statistics is a poor substitute for individual experience and the use of intelligence and judgment.

In this paper, with one exception, only the experiences of individual men or individual hospitals is presented, and an effort is made to assess the various factors which are believed today to enter into the risk of repeat section. After "the consideration and inference of individual results"<sup>12</sup> and an assessment of the present-day mortality of the repeat operation, a way to reduce this risk will be offered. The factors which enter into this mortality will be pointed out in two ways: (1) by conclusions of individual hospital studies, and (2) by a demonstration of additional factors generally believed to enter into the mor-

*transitory uterine ischemia* is a necessary concomitant of conversion of the conceptus from an ovoid to a cylindrical shape, the possible consequences of abnormal manifestations of this on the welfare of the maternal organism, of the fetus, or both is suggested.

2. The essential application of this discussion to practical obstetrics is that it emphasizes the physiologic basis of proper change in shape of the uterus for normal pregnancy particularly about the beginning of the last trimester of pregnancy.

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TABLE 1

NAME	HOSPITAL	YEAR	TOTAL REPEATS	NO. DEATHS (all classicals)	PERCENT DEATHS (4%, of classicals done)	TOTAL NO. SECTIONS total % deaths	DETAILS OF FATAL CASES
H. B. Matthews and A. S. Acken, Jr.	Methodist Brooklyn	1920 to 1938	330 301=2nd 9 deaths 22=3rd 2 deaths 7=4th 0 deaths 254 classicals	11 (all classicals)	3.3 (4%, of classicals done)	1,066 total % deaths 3.2	1 + 2 = cardiac deaths 3 + 4 = pulmonary embolus 5 = hemorrhage 6 = sepsis 7 + 8 = intestinal paresis 9, 10 + 11 = intestinal obstruction 3 also had ruptured uterus
K. M. Wilson	Johns Hopkins	1902 to 1925	88 69 patients 52=2nd 15=3rd 2=4th	3	3.4		1 hemorrhage—3 type 2 peritonitis—1906—classical late in second stage 3 peritonitis—intestinal injury from freeing adhesions
R. W. Mohler	Philadelphia Lying-In	1932 to 1942	299 (Sterilization at 2nd section as a policy)	5	1.7	1,322 949 classic 256=Kerr 68=Beck total % deaths 1.37	G-O-E anesthetics 1 Act 29—1 previous classical section—pulmonary embolus 15 days p.o.—4 hours of labor 2 Act 24—shock during op.—probably from anesthetic 3 1 previous section—shock + hemorrhage at op. 4 Act 34—3 previous classical sections—nephritis—lobar pneumonia
K. Knider	New York Lying-In	1930 to 1932	46 20=2nd 14=3rd 1=4th (low) 1=5th (classical)	1 following classical section	2.0		1 Act 40—severe diabetic—1 previous classical—severe p.p. hemorrhage—packed from below—died 3 hr. p.o.—no transfusions
J. L. Montgomery	Jefferson Medical College Philadelphia Hospital	1925 to 1936	46 35 classicals	2	4.3	229	1 sepsis 2 chronic nephritis and pneumonia
W. B. Thompson	Los Angeles Sundry	1923 to 1929	197 (100 sterilized) 180=2nd 15=3rd 2=4th 1=5th	8	4.0	1,225 305 sterilizations total % deaths 4.2	1 ruptured scar at 7 mo.—hemorrhage and shock 2 ruptured scar after 2½ hr. of labor—hemorrhage and shock—preventable 3 + 4 operative shock 5 intestinal obstruction—reoperated 2nd day 6 pulmonary embolus 11th day 7 toxemia and previous separated placenta—died of p.p. eclampsia 8 hysterectomy—hemorrhage from uterine artery—preventable



tality, but not stressed in the original papers. All of the papers whose results are summarized in Table I deal with sections as a whole and repeat cesareans, but for a few notable exceptions immediately to be mentioned, receive only cursory attention.

- Table I includes these exceptions. Smith<sup>14</sup> found that the mortality of primary section for uncomplicated disproportion or cervical dystocia was about 1 per cent in his series, whereas the risk of the repeat sections was 3.4 per cent. He stated: "It is difficult to say what the factor may be that makes repeat section a greater risk than primary section for uncomplicated disproportion." He pointed out that organic diseases such as rheumatic heart disease, nephrosclerosis, and the like, did not account for the difference. He found that "shock and hemorrhage—are a conspicuous cause of death in the group of repeat sections." (It is important to state here that his study and those immediately to be mentioned deal with classical sections.) Fraser and Sparling<sup>15</sup> agree with Smith. Hawks<sup>4</sup> and Matthews and Acken<sup>16</sup> also agree with the aforementioned. At first thought it might seem that the operative era of the cases in Table I was one in which a technique comparable with the present-day practice had not developed, but a careful analysis reveals that this is not true in the series of the Jewish Hospital of Brooklyn,<sup>17</sup> the Nursery and Child's Hospital,<sup>4</sup> and the Johns Hopkins Hospital review.<sup>18</sup>

A glance at the details of fatal cases shows that occasionally, as was the not infrequent habit from 1918 to 1928 or thereabouts, the patient was allowed to have a short period of labor. Occasionally also, the membranes had been ruptured four to six hours. These two factors increase the risk of peritonitis or septicemia. Ether was the commonly used anesthetic. The present extensive use of local, single, or fractional spinal, and pentothal with or without local, is a proof of the desire to get away from ether. The common occurrence of shock and hemorrhage is to some extent due to general anesthetics. They are much less common with local or spinal anesthesia. Occasionally death occurred from peritonitis, and various forms of tubal sterilization had been performed. No doubt in many other fatalities sterilization was performed, although it is not always recorded in the sometimes scanty summaries. Rupture of the classical uterine scar and adhesions become progressively more threatening with each operation. Generally, the studies neglect to state how many previous sections had been performed. However, enough data is given to enable one to conclude, together with one's knowledge of the almost universal practice of sterilization at the second or third section, that most of the sections were second sections, a few tertiary, and practically none beyond this. Thus, of 662 repeats, 553 were second sections, and only 66 were third sections. Only Smith's<sup>14</sup> series differed. Here, of 643 sections, 446 were second sections, and 197 third or more.

Table I indicates that repeat classical section is a dangerous procedure. No doubt the mortality is lower than 3 per cent if the operation is performed electively before rupture of the membranes and doubtless, too, the avoidance of general anesthesia will reduce the incidence of hemorrhage. It is obvious too that the sulfonamides and penicillin, and the more liberal and precise use of transfusions will materially lower the mortality. On the other hand no one knows what is the frequency of rupture of the uterus at the third or fourth section and its mortality, nor has the danger of adhesions ever been reported in a similar large series of repeat sections. There is every reason to believe, however, that following the classical technique, rupture and adhesions are just as dangerous today as ten or twenty years ago. Moreover, in the truly repeat operation (third section or more) certain constitutional factors be-

come operative which increase the risk as compared with primary sections. (1) The patients are older. They have passed their prime from the surgical standpoint. Hennessey,<sup>19</sup> Barrett,<sup>9</sup> and Orengo<sup>6</sup> believe that from thirty years of age onwards the mortality increases proportionally and is most elevated when the patient is forty years of age or more. (2) Dieckmann and Daily<sup>20</sup> have shown that multiparity is one of the factors predisposing to blood loss, due, they believe, to fibrosis or other changes in the uterine wall. This tendency plus ether anesthesia, may explain the frequency of hemorrhages in repeat operation.

The writer has not had difficulty with hemorrhage at primary sections but on five occasions has felt it wise to remove the uterus because of atony either with or without extension of transverse incisions. It is also his impression that excessive hemorrhage at repeat section is more common in hypertensives, nephritides, and cardiaes, a group not uncommon in section statistics. And (3) repeat section on patients in this last group becomes increasingly more dangerous because frequently the natural history of their diseases is such that they become poorer risks as they grow older. It may be safely assumed that the mortality of repeat classical section today can be definitely reduced from 3.2 per cent reported in Table I. Truly elective section with no labor, with the avoidance of inhalation anesthetics and performed in hospitals with well-stocked blood banks should show a reduction in mortality to one-half this or possibly more. Rupture of the scar is variously said to occur in about 4 per cent of cases. A mortality of 11 per cent, which is the average figure reported, would entail an unavoidable 0.5 per cent risk in repeat classical section from this source alone. The dangers of adhesions and hernia also cannot be avoided. Their exact contribution to the risk in terms of percentage is unknown. Were it only one-half that of rupture, these two sources alone—rupture of the uterus and adhesions or incisional hernias would give an unavoidable 0.75 per cent mortality, and this in cases for the most part being operated upon merely for the second time. If we were dealing with truly repeat sections composed of many third and fourth sections, these factors would no doubt ensure an inescapable mortality nearer 1 per cent. Where the improvement in mortality will occur is in the avoidance of sepsis, hemorrhage and/or shock, and pulmonary complications. Today, if the patient is operated upon by competent hands and in the properly equipped hospital, these dangers in a second classical section should not give rise to more than 0.75 per cent mortality. There are logical reasons, therefore, to believe that today the mortality of repeat classical section can be halved from 3.2 per cent of published experience to about 1.5 per cent. This is still a high price to pay for the privilege of having a baby, and the common belief of the past that repeat classical sections are dangerous seems justified by published experiences. The remedy proposed and commonly practiced in this country has been sterilization by various forms of tubal procedures. Whether these tubal resections best solve the problem will soon be discussed.

Table II reveals a far different picture. The chief new factor introduced is the low section. All of Greenhill's<sup>21</sup> were low sections. Approximately 75 per cent of the cases from the Boston City Series<sup>22</sup> were low. About two-thirds of Barrett's<sup>9</sup> were low, and, of 191 repeat sections of type unspecified, only one of five deaths occurred in a low section, and this was not elective. Of the total 972 repeat sections, 773 were second sections. Only 134 were third cesareans. In addition (chiefly from the Boston City Hospital) 31 had four sections and 10 had more than four. Sterilization was generally practiced at the second operation, and nearly always at the third (except in the Boston City Series). The mortality of the repeat cesareans was 13 deaths, or 1.3 per

J. A. Smith	Boston Lying-in	1894 to 1932  '94-'14 '14-'22 '22-'32	643 (on 446 patients) 446=2nd 197=3rd or more  84 262 297	22  2 10 10	3.4	1,556 total % deaths 4.9	7 due to sepsis 7 shock and hemorrhage 4 lobar pneumonia 1 intestinal obstruction 2 bronchial pneumonia 1 pulmonary edema and cardiac dilatation
A. J. Skeel and E. F. Jordan	Four Cleveland Hospitals	1927 to 1931	194	8	4.0+	322 (not in labor over 12 hr.) total % deaths 1.96	3 cases of ruptured uterus 4 cases of intestinal obstruction related to dense adhesions 1 p.p. hemorrhage at 4th section ? of myo- metrial syphilitic changes
J. R. Fraser and D. Sparling	Montreal Royal Victoria	1927 to 1936	124	4	3.2 216 elective primary with 1.3% mortality	562 total % deaths 3	N.B. 406 classicals 106 low cervicals generally after labor
J. Daichuan and W. Pomerance	Jewish Hospital Brooklyn	1908 to 1932	180	4 (none in 72 up to 1914)	2.2	733 (151 elective primary with 1 death) total % deaths 3.4	1 1920—2nd section—membranes ruptured 6 hr.—classical—died of peritonitis on 6th day 2 1921—3rd section—classical plus steriliza- tion—died 3rd day of peritonitis 3 1928—2nd section—membranes ruptured 4½ hr.—labor 2½ hr. classical plus steril- ization—died 4th day—embolus 4 1930—2nd section—elective classical plus sterilization—died of sepsis on 7th day
E. M. Hawks	Nursery and Child's New York City	1910 to 1920	114 (only 11 previ- ous to 1920= no deaths)	4	3.4	582 (492 classi- cal)	1 1923—2nd section—died 3 hr. p.o.—hemor- rhage and shock 2 1927—2nd section plus salpingo-oophor- ectomy—died of hemorrhage from injury to vein. 3 1927—2nd section—died of tbc. meningitis —probable contamination from spinal needle 4 1927—2nd section—died of pneumonia
J. P. Hennessy	St. Anne's New York City	1928 to 1941	90	2	2.1	316 (287 classi- cal) total % deaths 2.53	1 Aet 30—gravida iv—3rd section 5 hr. labor—5 cm. rupture of scar—repaired— died of peritonitis on 5th day 2 Aet 33—gravida iii—2nd section—died of peritonitis—(one other ruptured uterus recovered)
Totals			2352	74 (66 with data)	3.15		Sepsis responsible for 30% Hemorrhage and/or shock=24% Pneumonia=15% Ruptured uterus=10% Intestinal obstruction=9.12% Cardiac=5% Anesthesia=3%

cent. But if Barrett's series is excluded (because four of the deaths were in classical cases) there are 781 cases with eight deaths, or slightly over 1 per cent.

It is well known now that rupture of the uterus and adhesions are much less common after the low section than the classical operation. Just how common rupture after the low section is, is hard to say. Dieckmann<sup>11</sup> recently reported 7 in 1,800 cases, a frequency of 0.4 per cent. This is the frequency at the *second* section with a small number of third sections. The vertical incision was used. The figure would be higher if a large number of third or fourth sections were reported. Adhesions of the intestines to the uterus are uncommon after low section. On two occasions, however, the writer has found adhesions of the bladder and lower part of the uterus to the lower part of the abdominal wall so that a classical incision seemed advisable. If this happens, the patient, in the future, assumes the risk of classical repeat section. It seems safe to state, from the results of Table II, that the risk of a second or third low section is about 1 per cent. It also seems safe to assume, because of the factors already mentioned which operate in older patients, and because the risk of rupture will increase with each incision, that this mortality of slightly over 1 per cent at the second and third low section will rise somewhat with each repeat operation. How great the cumulative risk is we do not know. Even 1 per cent is not inconsiderable. It has been said that for the unfortunate who is this 1 per cent, the mortality is 100 per cent. No doubt the mortality will be reduced in good obstetric practice below 1 per cent for the second or third section. Dieckmann<sup>11</sup> believes that the low elective operation, "can be performed with a maximum mortality of 0.2 per cent. . . . Other indications are usually accompanied by an increased mortality but the increase should be due to the complication not to the operation." But these complications are not infrequently present and are often *inevitable* in the repeat section. At the present time there is no good reason to believe that large numbers of third, fourth, or fifth sections will show a mortality below 1 per cent. On the contrary, there are reasons to believe that it will be greater.

Table III summarizes the experience at St. Elizabeth's and the Cambridge Hospitals. Three hundred sixteen repeat sections were performed on 213 patients. The mortality was three patients (1 per cent). Where the type of section could be ascertained (some of the previous sections had been performed elsewhere), 75 were classical and 131 low. Although there was a total of 316 repeats, 143 (almost half) had only one repeat operation; 65 had two repeat sections; only 26 had three repeat operations; nine had four; and one had five repeat sections. Therefore, the factor of repetition is not marked in many patients. However, some impressions were obtained from the study. In 57 patients (15 per cent) adhesions complicated the performance of the operation and not by any means following the classical alone, although more commonly after the latter. Incisional hernias had to be repaired in four patients. Very thin uterine scars were found in six patients and in two additional women there were small ruptures present at the elective operations. In eleven cases there was atony of the uterus with hemorrhage. One required hysterectomy. Seven had "considerable bleeding." It is not clear whether these were simple atony or hemorrhage from uterine incisions or a combination of both. One died of postpartum hemorrhage. One patient had severe sepsis and was fortunate to recover. Three had phlebitis. At the Cambridge Hospital seven sterilizations were performed at the second section, four at the third cesarean, and three at the fourth operation. This series then reveals adhesions, thin scars, atony, and hemorrhage, and incisional hernias as complicating factors as do other cesarean series. They would probably have been more common had a larger number of third, fourth, and fifth sections been

TABLE II. CHIEFLY LOW SECTIONS

NAME	HOSPITAL	YEAR	TOTAL REPEATS	NUMBER OF DEATHS	PERCENT DEATHS	TOTAL NUMBERS OF SECTIONS	DETAILS OF FATAL CASES
C. J. Duncan and J. B. Doyle	Boston City	1926 to 1936	308 193=second 76=third 26=fourth 10=fifth 2=sixth 1=ninth	3	1.0	703 (550 were low cervical) total percent deaths 4.3	1 no labor—peritonitis 2 no labor—bronchial pneumonia 3 four-hour labor—membranes intact—pulmonary embolus 15 minutes post operatively Types of section not recorded
J. P. Greenhill	Chicago Lying-in	1915 to 1930	127 106=second 9=third 1=fourth	2	1.6	874 (all low) total percent deaths 1.26	1 gravida iv—three previous low sections— anemia of pregnancy—low cervical plus sterilization—died 8th day of peritonitis 2 Aet 34—gravida ii—second low section: obese—membranes ruptured 48 hr.—pre-operative temperature 100° F.—died of peritonitis on 5th day—preventable
E. M. Lazard	Personal in Los Angeles Hospitals	1903 to 1938	108 101=second 4=third	1	1.0	507 (355 low cervical) total percent deaths 1.57	1 respiratory paralysis following spinal an- esthesia—dose not stated
T. H. Kelly	Personal cases of R. K. Smith in Los Angeles	1907 to 1936	228 207=second 19=third 2=fourth	2 (218 sterilizations with 2 deaths)	0.9 0.9	894 (559 low cervical) total percent deaths (15 deaths) 1.7	1 pneumonia 2 ? embolus—?—collapse of lungs—no other data
R. L. Barrett	Woman's Hospital in State of New York	1923 to 1938	191 163=second 26=third 2=fourth	5	2.62 1.84 1.69 ----	912 620—low 235—classical total percent deaths 2.96	No data except four deaths after classicals and one after a low cervical—one had labor for 24 hr. with ruptured membranes and anemia—transfused ? type of operation—probably low
Totals			951 773=2 sections 131=3 sections 31=4 sections 10=5 sections 2=6 sections 1=9 sections	13	1.37		

in reports of the efficacy of operative techniques suggests a preoccupation with the particular techniques so marked as to exclude a broader viewpoint of the patient's safety. Fox,<sup>28</sup> reporting on 645 sterilizations at the Boston Lying-in Hospital from 1916 to 1937, failed to mention the mortality in those associated with cesarean section of which there were 152. But Smith,<sup>14</sup> from the same hospital, reported 559 repeat sections from 1914 to 1932 with a mortality of twenty, or 3.2 per cent. A conservation section plus tubal sterilization is not a "success" if the patient dies. Irving<sup>29</sup> (Boston Lying-in Hospital), has stated: "Should the mother die it is a tragedy." An analysis of these reports from Lull,<sup>30, 31</sup> Barrett,<sup>9</sup> and Adair and Brown<sup>32</sup> reveal about the same mortality as Table II and, in fact, Table II is composed mostly of cesareans plus sterilization (with the exception of the Boston City Series).

The answer then as to whether cesarean section plus tubal sterilization has a very low morbidity and mortality is in the negative, for a 1 per cent to 1.2 per cent mortality for an elective procedure is a high mortality today compared with other types of lower abdominal laparotomy. Does tubal sterilization avoid pathologic developments in the uterus? Obviously not. For the sake of the dubious advantage of menstruation, an organ robbed of its reason for existence is allowed to remain as a possible prey to pathologic changes. This bespeaks a short-sighted surgical vision dimmed by a false sentimentalism. Loomis<sup>33</sup> remarked: "If the fundus is removed (at repeat section) there is something in knowing that the excessive flowing of the abnormal menopause, the possibilities of fibroids and adenocarcinoma of the fundus, and the nuisance of comparatively useless menstrual periods are all forever gone." Lazard<sup>23</sup> and Watson<sup>25</sup> have expressed themselves in a similar fashion.

The procedure which will most surely lessen the immediate and remote dangers of the repeated section is cesarean hysterectomy. It fulfills the requirements. (1) It is simple of performance according to Williams,<sup>34</sup> Shears,<sup>35</sup> Lazard,<sup>23</sup> Schumann,<sup>13</sup> Stander,<sup>36</sup> Newell,<sup>37</sup> Harris,<sup>38</sup> and Phaneuf,<sup>39</sup> all possessed of familiarity with the operative technique. A false conception of the difficulties and dangers of the operation exists because of its infrequent performance. If familiarity breeds contempt, unfamiliarity sometimes engenders an unwarranted awe. (2) Is the morbidity and mortality low? There are no reports of very large numbers of elective section, but Lazard<sup>23</sup> and Greenhill<sup>21</sup> have reported no mortality in their experience, and morbidity reports from series of cases performed on poor risks (infection and the like) are striking in one respect. All emphasize in almost identical phrases the statement of DeLee and Greenhill<sup>40</sup>: "Recovery is more prompt, less painful, and less complicated than after the ordinary cesarean operation." Harris,<sup>38</sup> Phaneuf,<sup>39</sup> Watson,<sup>25</sup> Lash and Cummings,<sup>41</sup> and the Potters<sup>42</sup> share this viewpoint. Williams,<sup>34</sup> the leader of his day, stated flatly that "supravaginal amputation is safer and can be done more rapidly than the conservative operation followed by excision of the tubes." In 1928 he stated: "Early in my career, I recognized that convalescence following cesarean section terminated by supravaginal hysterectomy is much more satisfactory than after the apparently simple conservation (classical) operation." And, recently the Potters<sup>42</sup> expressed themselves similarly. So far all writers have given preference to supracervical hysterectomy over complete. In view of recent gynecologic experiences with the latter, and its advantages in eliminating future cervical cancer, this viewpoint may have to be re-examined. All stress the remarkable simplicity of the convalescence. The writer has analyzed 32 cases from the Cambridge Hospital and St. Elizabeth's Hospital. Seven were personal cases with assistance at two others. The same easy convalescence was noticed as described by other men. Notwithstanding the usual bad features (infection, ablation, hemor-

TABLE III

HOSPITAL	YEAR	TOTAL REPEATS	NUMBER OF DEATHS	TYPE SECTION	COMPLICATIONS	DEATHS
Cambridge and St. Elizabeth's Boston	1935	316	3	207 known	Adhesions	1 repeat low transverse cervical section—ether anesthesia—died of postoperative hemorrhage 20 hr. post partum
	to	Cambridge	Cambridge	131 low cervical	in 57	
	1945	109	0	76 classical	Very thin scars = 6	
		St. Elizabeth's	St. Elizabeth's		Incisional hernias = 4	2 repeat low section—GOE anesthesia—severe pyelonephritis—died 6 days post operative—autopsy—peritonitis—multiple small abscesses of kidneys
		207	3=1.5%		Rupture of scar = 2	3 one previous section—low under spinal (9 mg. pontocain)—respiratory failure on table—died 48 hr. later—never regained consciousness—autopsy—focal necrosis of thalamus from anoxemia
		143=second	Total		Sepsis = 4	
		65=third	3=1.0%		Bleeding or atony = 11	
		26=fourth				
		9=fifth				
		1=sixth				

done. None of the deaths were directly attributable to the fact that the operation was a repeat one.

The remedy proposed for the risk of repeat sections consists in various forms of tubal resection. These procedures effectively remove the danger of future repeat cesareans. The ideal remedy, however, should accomplish not only this but also (1) be simple of performance, (2) have the lowest immediate morbidity and mortality, and (3) lessen future risks from the possible development of pathology in an organ which, from the functional standpoint, has become useless. The various tubal procedures are rather simple to perform, although occasionally the control of oozing is said to be troublesome. Some require more operating time and anesthesia than section alone. As far as morbidity and mortality are concerned, certainly they do not decrease the mortality or morbidity of the conservative operation. The mortality will be at least that of the cesarean, classical, or low as the case may be. Lazard,<sup>23</sup> who has given a good deal of attention to this subject, believes that tubal sterilization adds to the risk because of the dangers of adhesions or the lighting up of infection. Dieckmann<sup>11</sup> advises cesarean hysterectomy in patients over 35 years of age. In answer to the question<sup>24</sup>: "Do you feel that cesarean hysterectomy is immediately a safer operation at the third section than any of the conservative types?" he replied: "We feel that cesarean hysterectomy is the safest operation." Watson<sup>25</sup> also favors cesarean hysterectomy over the conservative section plus tubal sterilization. In general, however, tubal procedures are favored and in fact seemingly considered innocuous.

There is a pardonable enthusiasm on the part of some men and clinics for a procedure which has originated with the particular hospital or surgeon. Enthusiasm may, however, dull the critical faculty. It is very difficult, if not impossible, to ascertain whether or not the addition of tubal resection to the conservative operation adds to the risk of the latter. Bishop<sup>26</sup> did not even mention mortality, and several years earlier with Nehms<sup>27</sup> in another discussion of the operative methods of sterilization stated: "This brief paper . . . is purely one of technique." One hundred cases of sterilization were reported. How many were accompanied by cesarean section is not stated. No mention is made of mortality in their own series although the statement is made: "In 1926 thirty-nine cases had been added to Madlener's first series making in all, excluding four deaths, 124 with no failure." The failure to mention mortality



This statement cannot be made of any of the conservative operations performed as repeat procedures for the reasons given, and because of the experience recorded. Believing the procedure to be safer and that the difference is probably 1 per cent, the opinion of a Catholic moral theologian was obtained in order not to transgress the religious beliefs and rights of Catholic patients. Ford<sup>47</sup> believes that a difference of 1 per cent mortality is a "very important difference, in fact a decisive difference" and stated in part: "The doctor must judge as best he can, that in this particular case the radical procedure is twice as safe." If one looks at the patient as a whole, as an entity in time, as an individual with a responsibility to a family and husband both now and in the future, it would seem logical to take both the present and future risks into consideration. Those who favor tubal procedures for sterilization seem rather unconcerned as to the future of these patients, or at least unaware of possible dangers. They perform a procedure that carries at least the same and probably a greater risk than the conservative operation, and which definitely fails to avoid possibility of danger in the future, when a procedure simple to perform and with a lower mortality is at hand—and a procedure which at the same time will eliminate future dangers. They have failed to see the forest for the trees. They have been too interested in ingenious little techniques and have lost sight of a consideration of the safety of the patient as a whole.

### Conclusions

1. A review of the experience of individuals or of individual hospitals reveals that the mortality of repeat classical cesarean sections in the country has been in the past 3.2 per cent. At the present time this risk probably can be reduced to about 1.5 per cent.

2. A review of similar experiences with the low operation reveals a mortality of slightly over 1 per cent. In both procedures, second cesareans bulk large with a much smaller number of third cesareans and practically none beyond this. It is highly probable that the danger would have been greater than 3.2 per cent in classical, and 1.2 per cent in low sections were a larger number of fourth and fifth cesareans recorded.

3. The dangers of elective repeat section are both immediate and remote. The remote dangers of rupture of the uterine scar and intestinal adhesions are very marked after the classical section, and exist to a much less degree after the low section. A conservative type of section with sterilization removes the dangers of rupture of the scar and risk inherent in another future section, but does not diminish the immediate mortality due to the procedure, nor the immediate and remote dangers from adhesions.

4. Evidence is presented that elective cesarean hysterectomy is simple to perform, causes less blood loss, has a smoother convalescence, and shows less morbidity than conservative repeat sections with or without tubal sterilization; and, in addition, eliminates future dangers from a useless organ, the uterus.

5. The procedure should be given much more consideration as an elective procedure at repeat sections, and should often be performed in the patient over 40 years of age; in the presence of poor scars; when the uterus does not contract perfectly; in the presence of marked adhesions; after the third or more classical section; and in patients who are subject to severe grades of



rhage, atony, etc.), 16 of the patients had no morbidity by the strictest of standards. Elective cesarean hysterectomy is safer than repeat elective conservative section of any type for several reasons. (1) It is a complete protection against the danger of operative and postoperative hemorrhage from the uterus. This danger is a very real one in repeat section. It was the greatest cause of mortality in Smith's series.<sup>14</sup> Some of the reasons for this have already been mentioned. Postpartum hemorrhage is not uncommon after cesarean section and yet as Slemmons<sup>43</sup> remarked: "Textbooks are silent and monographs on cesarean section and postpartum hemorrhage alike omit discussion of the subject." Marshall<sup>44</sup> stated: "Some degree of uterine atony is not always avoidable . . . deaths are unfortunately still recorded either from blood loss alone or the superadded shock of hysterectomy." I hardly need add these hysterectomies are not elective but are delayed and are performed in the presence of shock. (2) Cesarean hysterectomy greatly reduces the risk from sepsis and peritonitis. The introduction of the sulfonamides and penicillin in the conservative operations will in the future greatly lessen these dangers although sepsis will still be a factor. Dieckmann<sup>11</sup> stated: "No drug has been found to be effective in the cure of anaerobic streptococic infection." Cesarean hysterectomy will have the benefit of these drugs also and with their use serious infection in elective cesarean hysterectomy should be a rarity. (3) Montgomery<sup>45</sup> has stated: "Morbidity is the mother of mortality." The relationship is indivisible, and in a large enough series the operation with the lower morbidity will always show the lesser mortality. To the writer it is highly significant that those who have had experience with cesarean hysterectomy have noted time and time again that the convalescence is smoother and the morbidity less than after the conservative operation. DeLee and Greenhill<sup>40</sup> have attributed this to the absence of the puerperal necrosing uterus. The absence of distention, and pulse and temperature elevation is of great advantage and always of some importance. Their absence is of particular importance in patients suffering from a moderately advanced nephritis, cardiac disease, etc. Slemmons<sup>43</sup> studies led him to conclude that there is much less excretory load on the kidneys due to the absence of a puerperal uterus and that this is a factor of practical importance in severe nephritis. Lash and Cummings<sup>41</sup> stated that the operation is particularly indicated in pulmonary tuberculosis because the absence of the uterus means absence of the catamenia, and this has a favorable effect on the course of pulmonary tuberculosis. In comparison with the conservative operation plus sterilization Lazard,<sup>23</sup> Watson,<sup>25</sup> and Williams<sup>34</sup> stated that the danger of infection is less. Lazard,<sup>23</sup> with a considerable experience, stated: "The Porro procedure can be done in less time and with less shock than a tubal procedure." A few deaths from hemorrhage after conservative section have been reported in Tables I, II, and III. A hemorrhage occurred during the performance of sterilization by tubal procedure. In general, hemorrhage is an important factor in conservative repeat sections. Thompson and Krahulik<sup>46</sup> stated: "The control of hemorrhage during operation on a healthy uterus would seem to be a minor problem, yet this resulted fatally in four cases." And this was a review of 128 deaths of operations performed by specialists. There were four others who had hemorrhage after section. In addition, two more cases had shock probably from or with hemorrhage, and two others had shock after a low cervical section, in which hemorrhage may have been a factor. All of these difficulties are eliminated by hysterectomy. The mortality of elective cesarean hysterectomy should be well under 0.5 per cent. It should be no greater than that of any lower abdominal gynecologic procedure, simple in performance, done electively, and on the patients most of whom are in good condition.

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heart disease, kidney disease, or tuberculosis. Further experience may reveal it to be the procedure of choice routinely at or after the third section, even of the low type.

6. If the patient is a Roman Catholic and the surgeon believes that cesarean hysterectomy is, for that particular patient, a safer procedure than any type of conservative section, he may in the opinion of some Catholic moral theologians perform the operation. The uterus need not be pathologic to justify its removal.

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TABLE II. COMPARATIVE STATISTICS OF FETAL MORTALITY IN CESAREAN SECTION

YEARS REPORTED	NO. CASES	FETAL MORTALITY RATE	MATERNAL MORTALITY RATE	SOURCE OF REPORT
1920-1943	1,088	16.14%	5.07%	University of Maryland
1938-1942	500	9.2%	0.40%	Chicago Lying-in
1896-1942	1,333	6.0%	2.80%	Johns Hopkins
1926-1942	233	6.0%	2.10%	University of Iowa
1922-1944	362	4.4%	2.20%	Baylor Medical College
1935-1945	633	No Report	0.31%	New Haven Hospital
1936-1946	768	4.9%	0.65%	Methodist Hospital

TABLE III. CAUSES OF FETAL DEATH

	NO. CASES	NO. AUTOPSIES
Congenital anomalies	5	4
Prematurity	18	10
Macerated	4	2
Congenital atelectasis	3	2
Bronchopneumonia	2	2
Undetermined	2	0
"General congestion" (stillbirth)	1	1
Erythroblastosis fetalis	1	1
Hemorrhage of the newborn	1	1
Gastroenteritis	1	0
Total	38	23 (60.5%)

The maternal risk in cesarean section should not be increased even to minimize the fetal risk.

The actual causes of death of the infants in this series are listed in Table III. Twenty-three of the thirty-eight infants were autopsied and one congenital anomaly was so marked that it was an evident cause of death. This was a case of extrophy of the bladder, imperforate anus, and agenitalia. In three of the cases of congenital malformation the condition was discovered, or fully confirmed, only at autopsy and it may be that other anomalies were not discovered because of a lack of this examination. On the other hand, autopsy in the newborn is not always a conclusive examination, for some of the autopsies failed to disclose a perfectly satisfactory cause of death. The five congenital anomalies were all of such type as to be true causes of death. There was one other congenital deformity, a hare lip, but this was an incidental finding in a premature and was not of sufficient severity to be classed as even a contributory cause of death. The hare lip was the only abnormality found in the placenta previa group. Of the five congenital anomalies causing death of the infant, only one was of bony structure which might have been identified by preoperative x-ray examination.

Under the heading of prematurity in Table III are included only those infants whose deaths were considered to be due solely to prematurity or to prematurity and atelectasis. It does not include all the premature infants of the series. The babies varied in weight from 1,220 to 2,500 Gm., and all deaths occurred in the neonatal period, only one living more than twenty-four hours. The diagnosis was established at autopsy in 10 of the 18 cases. This percentage is low, and should be increased if we are to have completely accurate findings. The fact that an infant is premature is no contraindication to autopsy. Eleven of the eighteen deaths due to prematurity occurred after operation for placenta previa. Twelve of the babies in this group were delivered under regional anesthesia.

## FETAL MORTALITY IN CESAREAN SECTION\*

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IN 1939 Matthews and I reported a critical survey of the cesarean sections performed at the Methodist Hospital in Brooklyn from Jan. 1, 1920, to Jan. 1, 1938. It was noted with some concern that there was, in that series, a fetal mortality rate of 5.2 per cent. Such a fetal loss seemed high for an operation which has been associated with the idea, either expressed or implied, of fetal salvage. In comparing our fetal loss with that of others reported up to that time, however, it was found that ours was not unusually high. Within this past year it was decided to reascertain the fetal loss rate for a more recent period of time, to compare the findings with other recent reports, and to study the factors responsible for the loss. This present survey is an analysis of the fetal deaths in cesarean section at the Methodist Hospital for the ten-year period from Jan. 1, 1936, to Jan. 1, 1946.

In Table I are presented the general figures for this series and a comparison with the previously reported series. All infants of 28 weeks' gestation or over and all neonatal deaths up to the fifteenth day postpartum are included

TABLE I. MATERNAL AND FETAL MORTALITY IN CESAREAN SECTIONS  
(METHODIST HOSPITAL)

	NO. CASES	MATERNAL MORTALITY		FETAL MORTALITY	
		NO.	PER CENT	NO.	PER CENT
1920-1938	1,066	34	3.18	56	5.2
1936-1946	768	5	0.65	38	4.9

in the report. It will be noted that there has been a striking improvement in maternal mortality in the past ten years but that the fetal loss rate has remained almost unchanged. The improvement in maternal loss reflects, of course, the great stress placed on this phase of the subject. But there has been no such emphasis on the fetal loss associated with cesarean section. Most reports of the operation do little more than casually mention, and dismiss, the condition of the infant and some do not include it at all. It is hoped that emphasis on fetal mortality may help to reduce this loss.

A comparison of the fetal mortality rates in hospitals from different sections of the country is given in Table II. These figures are from recently reported series. It is interesting to note that there is no constant relationship between maternal and fetal mortality statistics. This fact was even more noteworthy in Table I, where the same hospital reported the two series, and where the marked reduction in maternal mortality was not accompanied by an improvement in fetal loss. It seems quite probable, therefore, that the same factors are not involved in the two mortality rates. In fact, in some instances, such as placenta previa, the factors appear to be antagonistic to each other.

\*Presented at a meeting of the New York Obstetrical Society, Dec. 10, 1946.

TABLE IV. INDICATIONS FOR CESAREAN SECTION IN CASES OF FETAL MORTALITY

	TOTAL CASES FOR INDICATION	FETAL MORTALITY		FETAL MORTALITY (LESS CON- GENITAL)	
		NO.	PER CENT	NO.	PER CENT
Placenta previa	56	14	25.0	14	25.0
Previous cesarean	272	9	3.3	7	2.5
Toxemias (no eclampsia)	31	5	16.1	4	12.9
Ablatio placenta	9	3	33.3	3	33.3
Contracted pelvis	259	3	1.1	2	0.7
Fetal distress	3	1	33.3	1	33.3
Previous vaginal plastics	11	1	9.0	0	0.0
Abnormal presentations (face, brow, transverse)	14	1	7.1	1	7.1
Elderly primipara	13	1	7.1	1	7.1

infants. Twelve of these fourteen deaths occurred in prematures and eleven of the deaths are ascribed to prematurity alone. Of these twelve deaths in prematures, eight of the cases were delivered under regional anesthesia and four under general.

The group of patients subjected to repeat cesarean showed a rather high fetal mortality. This included, however, two congenital anomalies and the three macerated stillbirths which have already been discussed. Of the remaining four deaths, three were due to atelectasis and one to gastroenteritis. All of these were neonatal deaths. The infants all weighed over 2,900 Gm. and were of thirty-eight weeks gestation or over. Prematurity was not a factor in this group of deaths.

All the patients subjected to cesarean section for toxemia were classified as pre-eclampsies. None had progressed to the stage of eclampsia. We employ cesarean section in toxemia only when there is a progressive condition which fails to respond to conservative treatment. The operation is further limited to those patients in whom vaginal delivery is not feasible, such as a primipara with a long, tight cervix. Patients who have progressed to the stage of convulsions are not considered suitable risks for cesarean section, and the operation is not advocated unless further complication, such as marked pelvic contraction, makes it imperative.

The babies that were lost in the toxemia group were all small, the largest weighing 1,575 Gm. There was one congenital anomaly. All of the deaths occurred in the neonatal period. The marked prematurity and the increasingly severe toxemia of the mother combined to make a decidedly unfavorable prognosis for these infants.

As would be expected, the infant loss rate is extremely high in ablatio placenta. It has been our policy to treat most of these patients conservatively. There is little encouragement in the fetal mortality statistics for the use of cesarean section, and vaginal delivery has given satisfactory maternal results.

There should be little fetal mortality among the patients operated upon for contracted pelvis unless operation is delayed unduly. In this series there were three deaths in the contracted pelvis group. One of these was due to a congenital anomaly. In another the cause of death was undetermined though it was suspected that the baby had a diaphragmatic hernia. The evidence was not conclusive, however, and autopsy was not performed. In the third case death was due to prematurity. The baby weighed 2,240 Gm. and was delivered under spinal anesthesia. Cesarean section was performed after three hours of labor with ruptured membranes. The mother had had two previous stillbirths in vaginal delivery. Her pelvis was an asymmetrical one with a tilt to the left

The care of the premature infant at the Methodist Hospital is given by qualified pediatricians. This is true for both ward and private cases, for it is felt that premature infants require this specialized care.

The four macerated infants exhibited no further cause of death. They comprise the bulk of the stillbirths. One of these four was clearly an instance of error in diagnosis. The cesarean section was done ostensibly for fetal distress but it is quite evident that any active distress had ceased before operation. The baby was extremely large, weighing 4,660 Gm., and the mother was a primigravida. The other three macerated stillbirths present a controversial point. All occurred in patients who had previous cesareans. We have followed the dictum of "once a cesarean, always a cesarean." This is done primarily as a maternal indication, and hence was followed in these cases despite the previous knowledge of a dead fetus in each instance. All of the babies weighed over 2,700 Gm. In two instances there was considerable justification for repeating cesarean section. One patient had had three previous classical cesareans with no vaginal deliveries. The other had had two previous classical cesareans and a myomectomy with no vaginal deliveries. In the third case the patient had had but one previous cesarean, a low flap type for placenta previa. This case might have been delivered vaginally of the fetus which was known to be dead.

The three cases listed as congenital atelectasis were all full-term infants. It is recognized that atelectasis, or insufficient expansion of the lungs, is a mere descriptive term and not a primary cause of death, but, in the two cases subjected to autopsy, no further findings were noted to explain the atelectasis. Both babies were delivered under spinal anesthesia. The third case was not autopsied, but review of the chart shows that the mother was operated upon because of previous cesarean section and had a prolonged ether anesthesia prior to the birth of the baby. This was probably the cause of the atelectasis.

The two babies who died of bronchopneumonia were delivered under spinal anesthesia. One was a premature infant weighing 1,362 Gm., and the other was a full-term infant weighing 3,632 Gm. Neither lived over twenty-four hours. The larger of these was the child of the elderly primipara whose operation was done largely to avoid fetal risk.

The two cases in which the cause of death was undetermined were full-term infants delivered under spinal anesthesia. One was a stillbirth, the fetal heart of which was heard definitely before operation, and the other was a neonatal death. This latter was suspected of having a diaphragmatic hernia, but the recorded evidence is inconclusive, and no autopsy was performed.

The death listed as "general congestion" was a stillbirth, the indication for operation being face presentation. The mother labored for twelve hours before operation was performed. This infant had a marked congestion of all the organs including the brain, and it is possible that this baby died as a result of the labor. Operation was done under local anesthesia.

The case of erythroblastosis fetalis occurred in a patient operated upon because of placenta previa. The baby was premature and lived only a few hours. The hemorrhage of the newborn occurred in a case of ablatio placenta. It also was premature and lived but a few moments. The case of gastroenteritis was a full term infant. This death has no obstetric significance but it should remind us that the type of delivery is no guarantee against future infections.

In Table IV are listed the indications for cesarean section in relation to fetal mortality. Because we have no control over congenital anomalies, a separate column was added excluding these cases. The fetal mortality in the placenta previa group is high, and it is largely a mortality of premature in-

A comparison of the viable fetal mortality associated with vaginal and cesarean delivery is given in Table VI. The relatively large number of stillbirths in cesarean section requires some consideration. Four of these were macerated infants. They have been previously discussed in this paper. The other two stillbirths exhibited a fetal heart before delivery and a heartbeat at delivery. Neither could be made to breathe. The cause of death in one of these was undetermined and autopsy was not performed. In the other the autopsy diagnosis was "general congestion." This was the face presentation which was subjected to twelve hours of labor. Both of these infants were delivered under spinal anesthesia. None of the stillbirths was premature, the smallest weighing 2,725 Gm.

Twenty-two of the neonatal deaths occurred in premature infants, and, of those infants expiring in the first twenty-four hours of life, eighteen were premature. This is in accord with other statistics of premature infants showing a high rate of fetal mortality shortly after delivery. The importance of care just prior to delivery and after delivery must be stressed in order to effect a greater saving of these small infants.

We have seen that a large part of the fetal mortality in cesarean section in this series has been the mortality of prematures and particularly prematures associated with placenta previa. The rate of premature mortality in vaginal delivery as contrasted with that in cesarean delivery is shown in Table VII. Cesarean section presents almost twice the premature fetal mortality of vaginal delivery. If the cesareans performed for placenta previa are excluded, however, the cesarean rate approximates that of vaginal delivery. In Table VIII these cases have been broken down into the various weight groups. It will be noted that the different weight groups are fairly proportionately represented in each type of delivery. In certain of these weight groups we are dealing with rather small numbers of cases so that a comparison of individual weight groups does present the possibility of error. However, the over-all picture is extremely suggestive of the fact that cesarean section for placenta previa carries with it an added risk for the premature infant, and that that risk is increased by some factor other than size of the infant alone.

TABLE VII. PREMATURE FETAL MORTALITY

	SURVIVED	DIED	MORTALITY RATE
Vaginal deliveries	500	139	21.7% (217 per 1,000)
Total cesareans	34	22	39.2% (392 per 1,000)
Cesareans less placenta previa	28	10	26.3% (263 per 1,000)
Cesareans performed for placenta previa	6	12	66.6% (666 per 1,000)

TABLE VIII. PREMATURE FETAL MORTALITY

	VAGINAL DELIVERIES			TOTAL CESAREANS			CESAREAN LESS PLACENTA PREVIA			CESAREAN FOR PLACENTA PREVIA		
	SURVIVED	DIED	MORTALITY RATE	SURVIVED	DIED	MORTALITY RATE	SURVIVED	DIED	MORTALITY RATE	SURVIVED	DIED	MORTALITY RATE
907-1,361 Gm.	15	44	74.5	3	3	50	3	1	25	0	2	100
1,361-1,814 Gm.	63	44	41.1	2	9	81.8	1	4	80	1	5	83.3
1,814-2,268 Gm.	263	35	11.7	11	8	42.1	10	3	23	1	5	83.3
2,268-2,495 Gm.	359	16	4.3	18	2	10	14	2	12.5	4	0	0
Total	500	139	21.7	34	22	39.2	28	10	26.3	6	12	66.6



as a result of an ankylosing lesion of the left hip following infection in childhood. The configuration was noted clinically and confirmed by x-ray.

Fetal distress as an indication for cesarean section occurred three times in the 768 operations. In each instance the patient was a primigravida who was operated upon early in labor for an abnormality in the fetal heart rate of such character as to indicate distress. It should be pointed out that great care must be exercised in these instances. In the macerated stillbirth occurring in this series, the maternal pulse was evidently mistaken for the fetal heart. There could have been no real fetal distress just prior to operation.

It is difficult to see any connection between indication for operation and fetal mortality in those patients operated upon because of previous vaginal plastics. These cesarean sections were all elective operations and were performed because of previous vaginal operations for repair of the perineum, anterior, and posterior walls and cervixes. Three of these patients had bad rectovaginal fistulas repaired prior to the cesarean section. The one fetal death in this group was due to a congenital anomaly.

The abnormal presentations, face, brow, and transverse, were treated by cesarean section fourteen times in this series. There was but one fetal loss, a face presentation subjected to twelve hours of labor and delivered under local anesthesia. The baby was a stillbirth weighing 3,175 Gm. Earlier intervention in this case might have given a more favorable result. The autopsy diagnosis was "general congestion."

Of the patients operated upon for the indication of elderly primipara, only one showed a fetal loss. This was a neonatal death of a 3622-Gm. infant delivered under spinal anesthesia. The autopsy diagnosis was bronchopneumonia.

In Table V are listed the types of anesthesia used in the cases associated with fetal loss. Regional anesthesia was used in 71 per cent of the cases and in 72 per cent of the prematures. This type of anesthesia avoids the danger of increased anoxia to the fetus.

TABLE V. TYPE OF ANESTHESIA IN CASES OF FETAL MORTALITY

	PREMATURE	FULL TERM	TOTAL
Spinal	13	9	22
Local	3	2	5
General	6	5	11

TABLE VI. VIABLE FETAL MORTALITY (1936-1946)

	TOTAL CASES	FETAL MORTALITY		STILLBIRTHS	NEONATAL DEATHS
		NO.	PER CENT		
Vaginal deliveries	18,016	652	3.6	420	232
Cesarean sections	768	38	4.9	6	32*

\*25 lived less than one day; 7 lived more than one day.

Spinal anesthesia affords far better relaxation of the maternal abdominal muscles, and in this respect has a distinct advantage over local anesthesia. This greater relaxation is an aid in the delivery of the fetus and is of particular importance in the case of the premature infant where ease of delivery plays so great a role in avoidance of trauma. It should be noted here also that the incision in the uterus must be of sufficient size to insure easy delivery of the infant. The maternal tissues are also subjected to less trauma where proper muscular relaxation is achieved, and it is our feeling that spinal anesthesia is an extremely valuable aid when given properly and under competent supervision. We now use general anesthesia only in those few cases where spinal is either refused or contraindicated. It should be avoided particularly in the delivery of the premature infant.

## Conclusions

1. Fetal mortality in cesarean section is higher than that for vaginal delivery.

2. An increase in autopsies on stillbirths and neonatal deaths is imperative in the interest of accurate diagnosis.

3. If cesarean is indicated in cases of abnormal presentation, operation should be performed early.

4. Regional anesthesia avoids one cause of fetal anoxia and should be widely used in cesarean section. Spinal anesthesia produces greater relaxation thereby aiding delivery and lessening trauma to the baby.

5. Prematurity is the greatest single cause of fetal mortality in cesarean section. It occurs most often in conjunction with placenta previa.

6. The policy of delay in active treatment of placenta previa might carry more infants closer to term, but widespread advocacy of this would endanger the present low maternal mortality.

7. In cases of maternal hemorrhage the mother should have early transfusion and the administration of pure oxygen to combat fetal anoxia. These procedures should be carried out even though there be no apparent need of them by the mother.

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## Discussion

DR. WILLIAM E. STUDDIFORD.—Most series of cesarean sections which have come to our attention have been analyzed from the standpoint of maternal mortality, and in most of them the fetal mortality is rather high. In many the outstanding cause of death is prematurity.

While a great deal of this fetal loss is due to factors such as placenta previa and toxemia which necessitate interruption of pregnancy before term, some is due to error in the estimation of the duration of pregnancy. It is often difficult to determine the expected date of confinement, especially in those patients who occasionally skip menstrual periods. The estimated date of confinement is very often false. In cases where the maturity of the baby is in doubt, it is probably wise to await the onset of labor before performing cesarean section.

DR. SAMUEL A. WOLFE.—There is one other point in connection with the treatment of placenta previa by cesarean section. With the delivery of the baby, the placenta may be traumatized with considerable loss of fetal blood from the vessels in the torn chorionic villi. It may be wise in placenta previa with a premature baby not only to give oxygen and maternal transfusion early, but also to give the baby a transfusion, if there has been considerable bleeding from the placenta, especially if there has been delay between the time of incision of the uterus and delivery.

DR. CLAUDE E. HEATON.—I think we should be grateful to Dr. Acken for keeping in mind the point that cesarean section does not guarantee a live baby. In 271 cases at the French Hospital there was a loss of 12 babies, or 4.4 per cent.

The subject of anesthesia should be emphasized. Many fetal deaths are not preventable, for example, those due to prematurity in toxic mothers. However, infants of large size are occasionally lost from poor anesthesia. Local or spinal anesthesia is valuable in selected cases.

I am sorry Dr. Studdiford did not go into the expectant treatment of placenta previa. On his service the expectant treatment has been quite successful, often providing the infant with a better chance of survival without extra risk to the mother.

Maternal hemorrhage is the major factor differentiating a cesarean section for placenta previa from the general run of cesarean sections. It is frequently difficult to estimate the extent of that hemorrhage, for the original bleeding occurs before the patient enters the hospital, and even the bleeding in the hospital presents a problem in accurate estimation except as the patient herself exhibits the effect of it. However, the fact that a patient is transfused is evidence that, in the opinion of the attending obstetrician at least, the bleeding has been excessive. In the cases of placenta previa subjected to cesarean section in this series, the operations were performed as promptly as possible after the hemorrhage. This was particularly true of those that had bled sufficiently to warrant transfusion. In these cases there was, of course, prompt matching of blood and prompt transfusion, but transfusions were started either at the time of operation or after operation. This meant that the replacement of maternal blood came either shortly before the delivery of the child or immediately thereafter. In either case the transfusion would have little effect upon the infant. In his book, *The Physiology of the New Born*, C. A. Smith states that "the respiratory characteristics of fetal and neonatal blood indicate the need for a sufficient if not an augmented supply of oxygen to the infant both during and after birth." Beck, in his paper, "The Obstetrician's Responsibility in Anoxia and Prematurity," states, "Anything which might reduce the oxygen content of the maternal blood—might well lead to anoxia in the fetus." In the conditions described, these premature infants have had a decreased supply of oxygen as a result of the maternal hemorrhage and the replacement has occurred after it is of little value to them even though the mother may be fully cared for by this replacement. Potter and Adair make the statement that "Primary anoxemia is always intrauterine in origin, although its effect may be such that the infant does not succumb until after birth." As confirmation of the effect of maternal blood loss upon the child, it was noted in the present survey that in those cases of cesarean section for placenta previa where maternal transfusion was necessary the fetal mortality was 52.9 per cent. In those cases of cesarean section for placenta previa where no maternal transfusion was given the fetal mortality was 15.4 per cent. There were no transfusion reactions and it should be recalled that the transfusions were given at such time as to have comparatively little effect upon the child, thus indicating that the maternal blood loss was a factor in the fetal mortality.

It is therefore suggested that maternal transfusion be given in all cases of hemorrhage as early as possible and as long prior to operation as is feasible, in order to avoid the increased risk of delivering a premature infant with the additional problem of anoxia induced by maternal blood loss. Pure oxygen should be given the mother so that the risk of anoxia in the infant may be further reduced. This should be started as soon as possible after hemorrhage occurs and continued to the time of birth in any case where appreciable bleeding has occurred. This procedure should not be dependent solely upon the condition of the mother but should be given in the interest of the child.

H. W. Johnson and Macafee have advocated delay in emptying the uterus in placenta previa. There may be some instances in which this is possible but to advocate delay as a general policy in placenta previa would seem to invite disaster. A very wide experience and fine judgment are needed to determine the case that might be delayed. It is granted, however, that such delay would, if successful, enhance the chances of survival of the fetus. The marked improvement in maternal mortality in placenta previa would be greatly endangered by widespread advocacy of this policy of delay.

No attempt is made in this paper to discuss the routine care of the premature infant, for that has been very ably covered by other authors.

## VAGINAL HYSTERECTOMY WITH RADICAL ADVANCEMENT OF THE UTEROSACRAL LIGAMENTS FOR PELVIC FLOOR HERNIOPLASTY IN CASES SHOWING THIRD DEGREE UTERINE PROLAPSE\*

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IT IS generally agreed that the numerous operations commonly used for the repair of third degree pelvic herniation, popularly called uterine prolapse, are not completely satisfactory since recurrences of the hernias are common, and unsatisfactory vaginas are a frequent end result. For this reason the authors have developed a technique which reinforces the sites of herniation and leaves an adequate vagina. To accomplish this, the strong fascial tissues of the uterosacral ligaments are fixed between the bladder with its fascial structures and the vaginal wall. They are attached to the arcuate pubic ligament on each side of the urethra in such a manner as to reinforce the pubo-cervical fascia so firmly that a recurrent cystocele, urethrocele, colpocele, or enterocele is rare.

For years the medical profession has been intensely interested in the relief and cure of uterine and vaginal herniations. Life often becomes quite intolerable to a woman when her pelvic organs become markedly prolapsed. This distressing condition usually interferes with urination, defecation, and coitus. Primarily, such a patient is interested in obtaining relief from the associated physical discomforts; when these are alleviated through a surgical approach, she remains disappointed unless restoration of the natural function of the vaginal canal is also attained. Any operation that interferes with normal coital relations is therefore unsatisfactory. With this restoration in mind many methods of repair have been devised, but a large variety of these have been found to produce end results which are not completely satisfactory.

\* \* \*

Most of the operations which have been proposed during the present century for the correction of uterine prolapse have produced high percentages of cures. However, according to current medical literature, the percentage of partial or total failures (as characterized by a recurrent cystocele, urethrocele, colpocele, enterocele, rectocele, or any combination of these hernias) ranges from 4 to 30 per cent where these various operations are used. Furthermore, even though no hernias redevelop, the end results with many of these procedures are unsatisfactory, as they produce vaginas which are very much shortened.

It then becomes obvious that as yet we have no ideal operation for the correction of uterine prolapse. Probably no single plan of reconstructive

\*Presented, by invitation, before the Chicago Gynecological Society, May 17, 1946.

†Deceased December, 1944.

DR. RALPH L. BARRETT.—I'd like to know what is meant by the expectant treatment of placenta previa.

DR. CLAUDE E. HEATON.—In answer to Dr. Barrett, I would like to cite the case of a woman who was about seven months' pregnant, who lost about 500 c.c. of blood. She was hospitalized for six weeks and then sent to a hotel until labor began. It would have been very easy, with the initial considerable loss of blood, to have done a section for placenta previa.

A patient with placenta previa can be safely observed provided she is in a good hospital with a blood bank and a good resident staff. If she can be carried over two or three weeks, you can sometimes guarantee a live baby.

On Dr. Studdiford's service we observe these patients until the baby is big enough, and then examine them in the operating room prepared to do section. I doubt whether we risk any lives that way.

DR. E. EVERETT BUNZEL.—The discussion gives the impression that cesarean section is about the only treatment for placenta previa. There is a great need for individualization of each patient, and there is a large number of patients who can be delivered vaginally who have placenta previa or even accidental hemorrhage, depending on parity and the condition of the cervix. Several years ago, Dr. B. P. Watson discussed this problem and showed that in many instances it was quite possible to deliver vaginally, and that the fetal mortality rate in selected cases was no greater than that associated with abdominal section.

DR. SAMUEL A. COSGROVE.—It is rather unfortunate that Dr. Bunzel should assume that the consensus of opinion in this Society is that every case of placenta previa should be subjected to cesarean section. Dr. Watson's estimation of the treatment of placenta previa would be largely approved by every member of this organization.

I perhaps misunderstood Dr. Bunzel, but if I understood him correctly, I want to dissent very emphatically with him in his assumption that anybody here has put forth the doctrine that placenta previa should invariably be sectioned.

DR. E. EVERETT BUNZEL.—I have no rebuttal to offer Dr. Cosgrove. However, I don't think he got the gist of my remarks. I do not recall anything in the presentation which referred to the vaginal delivery in placenta previa. I got the impression that cesarean section was advocated. There are many cases in which it is not necessary to do a section. There are also many cases erroneously diagnosed as placenta previa.

DR. ACKEN (Closing).—In answer to Dr. Studdiford, there were nine babies lost in the repeat cesarean section group in our series, none of them premature infants. The smallest baby in the group weighed 2,900 Gm. and was of 38 weeks' gestation. There was no loss from prematurity itself.

I think that the widespread advocacy of the expectant treatment of placenta previa as a general measure would do a great deal of harm. No doubt in competent hands it could be carried out safely, but I feel it should not be done as a general measure throughout the country.

I regret creating a wrong impression in the mind of Dr. Bunzel. We deliver many cases of placenta previa per vaginam but the patients under discussion tonight were simply those who had been delivered by cesarean section.

same purpose: after performing a vaginal hysterectomy in a routine manner and uniting the broad ligaments in the midline, the cystocele is corrected by incising the vaginal wall over the bladder from below upward, and the pubocervical fascia is dissected and sutured in the midline, following which *the uterosacral ligaments, previously dissected from the cervix and posterior fornix, are advanced and firmly attached to the arcuate pubic ligament on each side of the urethra.* Following this work the perineum is repaired as a routine procedure.

Before undertaking this or any other operation, sound surgery requires that a careful examination be made to establish the correct and full diagnosis. In the operation herewith proposed, the existence of large tumors, multiple adhesions, and active inflammations, as well as pregnancy, constitute obvious contraindications to surgery. In very obese and uncooperative patients an examination under anesthesia may be necessary to establish the diagnosis.

In transvaginal surgery, the importance of the preoperative preparation of the field of operation cannot be too strongly emphasized, since one of the authors some years ago observed two cases of fatal peritonitis following negligence in this regard. Our patients submit to the following routine after the onset of anesthesia. The perineal region and the vaginal outlet, together with the vagina and the herniating structures, are thoroughly scrubbed with soap and water and then painted with a standard antiseptic solution of known efficacy. The patient is draped, and then the vagina is swabbed with a 2 per cent iodine solution followed with 70 per cent alcohol.

### Technique

Three or more heavy silk sutures are placed through the anterior and posterior lips of the cervix in order to occlude the cervical canal as well as to afford a means of traction. An elliptical incision is made through the vaginal wall circumscribing the cervix just proximal to the bladder reflection, and 2 c.c. of pitocin are injected into the parametrial structures to minimize bleeding. The bladder is now separated from the cervix by blunt dissection, after which the posterior vaginal wall is freed and the uterosacral ligaments dissected (Fig. 1). They stand clearly as strong supporting structures, since they have usually hypertrophied because of prolonged stress in supporting the uterus. After these ligaments have been sufficiently dissected they are clamped, cut, and ligated at their junction to the cervix, but they are allowed to remain attached to the upper portion of the posterior vaginal wall. The sutures are cut long for use as guy ligatures. The posterior and anterior cul-de-sacs are then opened. Now the cardinal, broad, and round ligaments are successively approached and treated by clamping, cutting, and ligating them until the uterus is free and removed. The sutures on the round and upper broad ligaments are left long to serve as guy ligatures; tension on them is helpful in examining the adnexa at this time. If these organs are normal and no enterocele is noted, the peritoneum of the two cul-de-sacs is closed transversely with interrupted catgut sutures in such a way as to reduce the size of the posterior cul-de-sac (Fig. 2).

In the correction of the cystocele, and any co-existing urethrocele, the bladder is first separated from the anterior vaginal wall and the latter is cut in the midline to within one centimeter of the external urinary meatus. The pubocervical fascia is dissected from the vaginal mucosa on each side of the

surgery will ever be devised which will be applicable to all types of individuals seeking care for prolapse; obviously in cases where it is advisable to conserve the uterus for future pregnancy the treatment will usually vary from that offered a postmenopausal case. The surgeon will in the future, as in the past, undoubtedly have to individualize his patients and rely upon various surgical procedures to obtain the best possible end result for any given case.

### Anatomy

The anatomy of the female pelvis has been thoroughly studied during recent years and presented in detail by Curtis and his associates, rendering unnecessary any review of this subject at this time. However, for the purpose of this paper, it should be recalled that all the pelvic ligaments contain smooth muscle as well as connective tissue, and therefore are very prone to hypertrophy under the stress of constant pull such as occurs in prolapse. Because of this, one frequently finds the round ligaments and uterosacral ligaments thicker than normal in such cases—a fact which increases the value of these ligaments in any effective surgical reduction.

A second anatomic fact which bears accentuation at this time concerns the nature of the ligaments which form the upper boundary of the pubic arch. The subpubic ligament, or so-called arcuate pubic ligament, is a thick triangular arch of strong ligamentous fibers which connects the right and left pubic bones, and serves to round off the pubic angle. Below this arcuate pubic ligament lies a second ligament, the transverse ligament of the pelvis, which is composed of the fascias covering the inferior and superior surfaces of the urogenital diaphragm. This so-called transverse ligament of the pelvis extends from one side of the pubic arch to the other, and blends with the pubic arcuate ligament on each side. Both of these ligaments, especially the arcuate, are ideal for anchorage purposes in pelvic repair work.

### Operative Repair

A third degree prolapse is commonly defined as a descent of the uterus to the extent that the cervix or corpus uteri protrudes through the vulva. As a result of this the bladder and urethra are often pulled down from the symphysis pubis resulting in a large cystocele and a urethrocele. Likewise, the rectum is usually pulled down and forward producing a rectocele. Because the peritoneum of the posterior cul-de-sac may also be drawn down with the uterus, an enterocele may develop. Most gynecologists agree that a third degree prolapse, occurring in an individual past the age of menopause or in whom it is no longer definitely advisable to conserve the uterus, may best be corrected by removing the uterus together with all grossly diseased tissue, and closing the hernial sacs with a repair of the pelvic floor. Therefore, the uterus is removed, the posterior cul-de-sac greatly diminished in size, the cystocele reduced, and the urethral sphincter tightened if it shows relaxation, and the pelvic floor repaired.

In order to accomplish this, the writers developed the operation described herewith which differs as follows from other techniques advocated for the



herniation (Fig. 3). After advancing the bladder this hernia is then repaired with a series of Halsted mattress sutures of fine silk or chromic catgut begun just below the urethral orifice and continued posteriorly so as to approximate the fascia over the entire urethra. This series of sutures is continued posteriorly, bringing the pubocervical layers of fascia together in the midline, so as to support the infolded bladder (Fig. 4). The extremities of the pubocervical fascia are left free at this time.

By placing tension on the guy ligatures left on the round ligaments, it is possible to bring them into view at the site of the peritoneal closure. These ligaments are now sutured together over the closed peritoneum. Following this, the broad ligaments are also approximated in the midline by two or three interrupted sutures, and at this time the extremity of the pubocervical fascial sheet is sutured to them, effectually reducing the herniation of the bladder. Thus the fibers of the pubocervical fascia are anchored posteriorly to the other supporting structures of the pelvis.

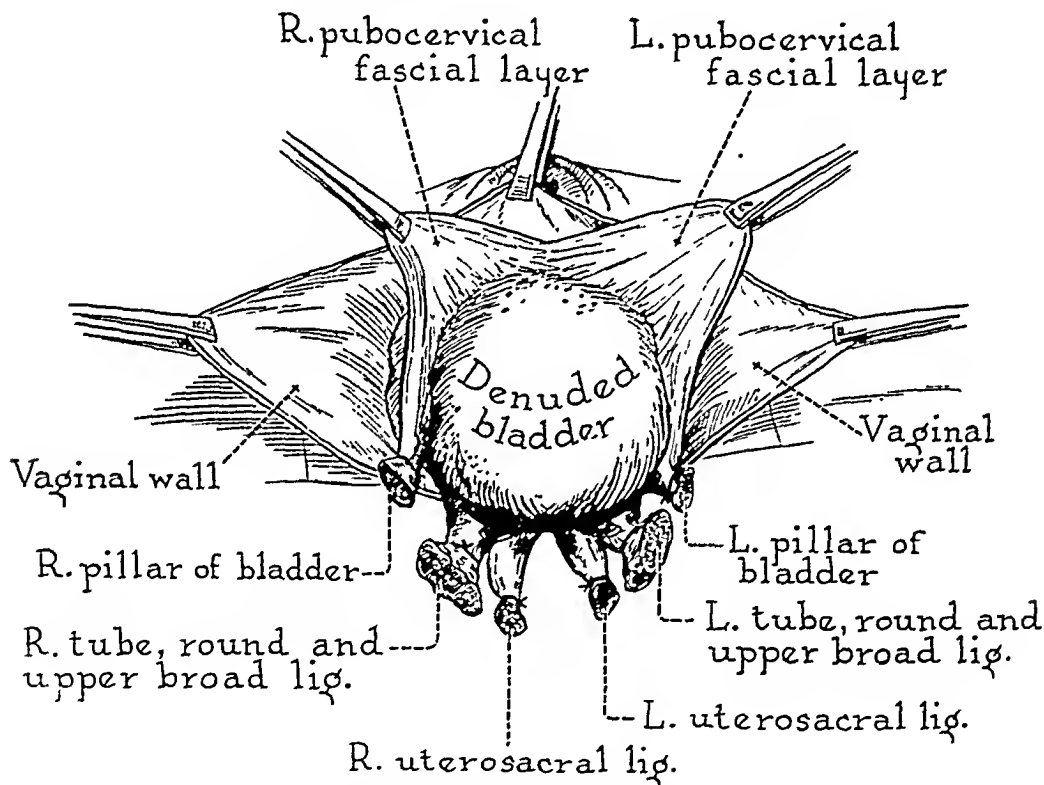


Fig. 3.—After closure of the peritoneal cavity a midline incision is made in the anterior vaginal wall and the bladder dissected free. It is then advanced upward and a flap of pubocervical fascial tissue is separated from the vaginal wall on each side. These flaps are later utilized in the repair of the cystocele and urethrocele.

To further insure against a recurrence of the cystocele, the ends of the mobilized uterosacral ligaments are now advanced to the subpubic arch on either side of the urethra (Fig. 5) and sutured to the thick arcuate pubic ligament. The uterosacral ligaments are then approximated in the midline, beginning just below the urethra and extending back toward the rectum as far as possible; in this process they also are anchored to the round and broad ligaments (Fig. 6).

This procedure obliterates the hernias of the anterior and posterior cul-de-sacs, and enhances the supporting structures of the anterior portion as well as the posterior portion of the pelvic floor. The uterosacral ligaments become a substantial accessory to the anterior fascia of the vagina. The same results



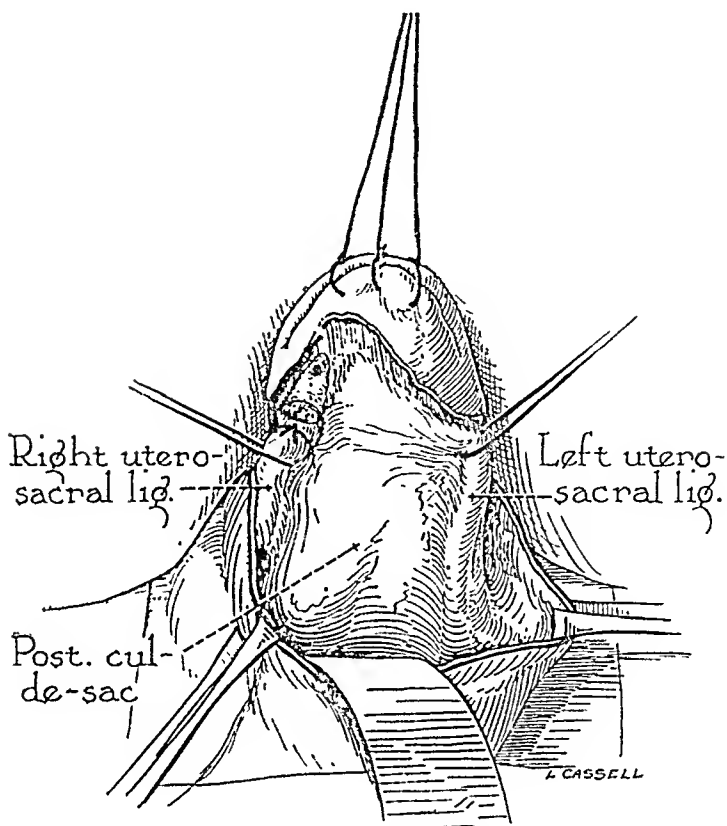


Fig. 1.—Schematic drawing of a prolapsed cervix showing three heavy silk sutures which have been placed through the anterior and posterior lips of the cervix so as to occlude the canal. The sutures are left long for the purpose of traction. After making an elliptical incision through the mucosa of the cervix just below the level of the bladder reflection, the insertion of the utero-sacral ligaments to the cervix can be noted posteriorly. These ligaments are dissected, clamped, cut, and tied as seen on the right in this drawing.

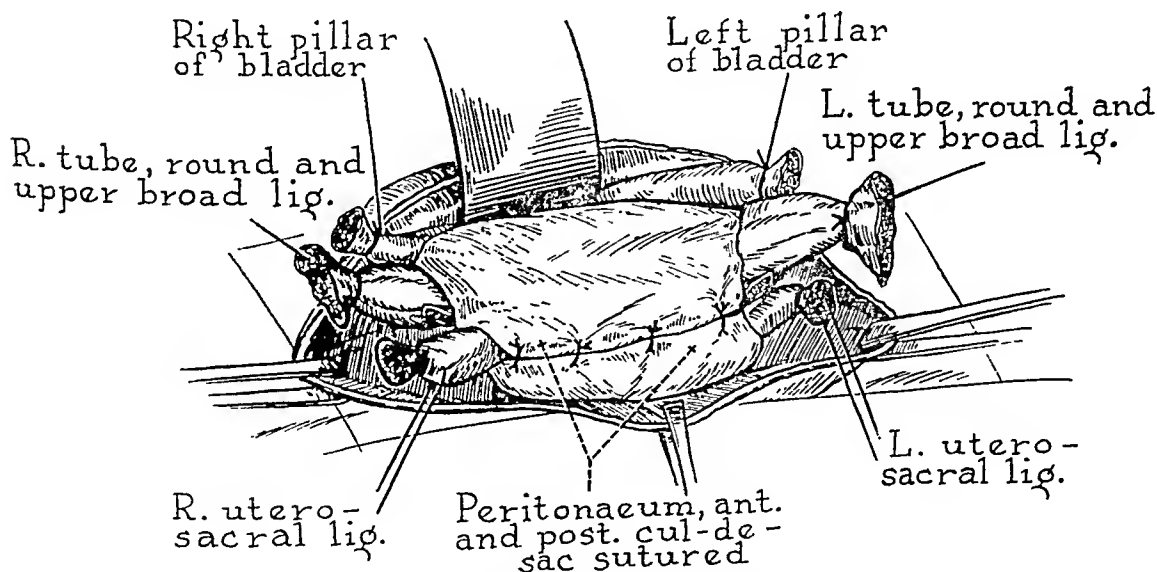


Fig. 2.—Following the routine vaginal hysterectomy, the peritoneal reflections of the anterior and posterior cul-de-sacs are approximated with a row of interrupted catgut sutures. At each lateral angle the cut edges of the broad and round ligaments can be seen to emerge from the peritoneal cavity. Lying extraperitoneally are the pillars of the bladder anteriorly and the uterosacral ligaments posteriorly.

can be achieved by placing the uterosacral ligaments deep rather than superficial to the pubocervical fascia. Although this appears to be more anatomical, it is a little more difficult technically, and, in so far as it obviates the opportunity of attaching the pubocervical fascia and so-called pillars of the bladder to the stumps of the round and broad ligaments, it appears to us to be a less desirable procedure.

When the uterosacral ligaments are extended to the pubic arch, the posterior vaginal fornix is displaced tending to shorten the anterior wall. To compensate for this, the vaginal wall at the fornix is separated from the uterosacral ligaments which are dissected free as far back as needed. The anterior colporrhaphy is now completed by trimming the excess anterior vaginal mucosa and approximating the cut edges in the midline with interrupted sutures of fine chromic catgut; many of these sutures are so placed as to catch the underlying uterosacral ligament layer.

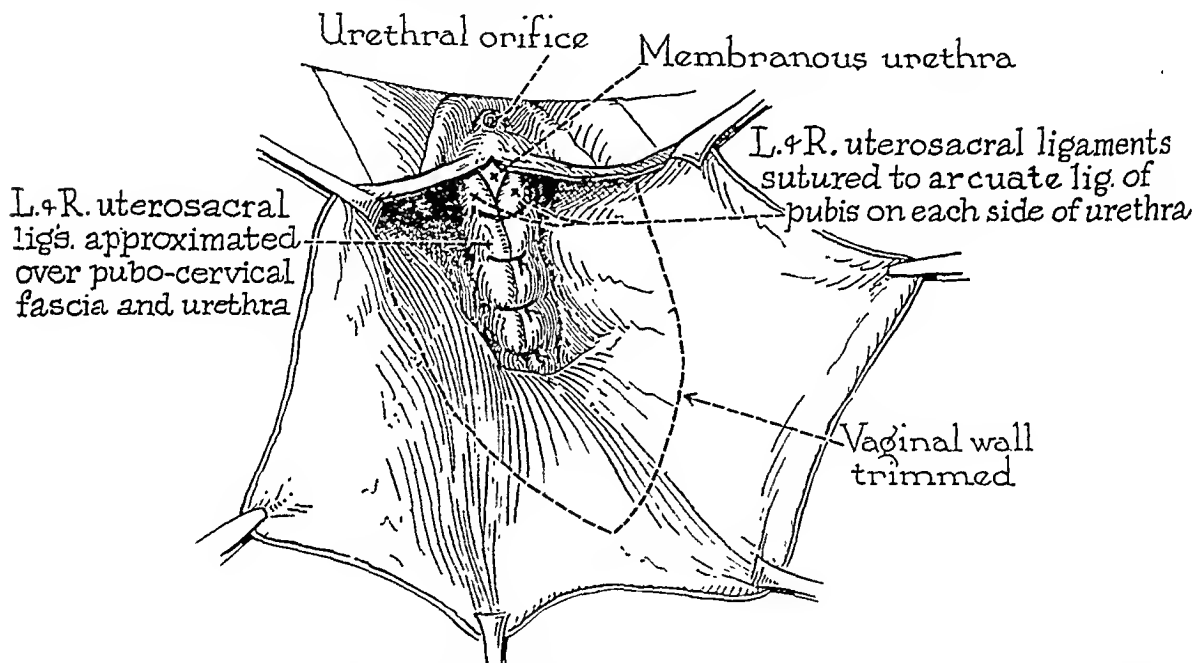


Fig. 6.—After the ends of the uterosacral ligaments are fixed to the arcuate pubic ligament, their free edges are approximated in the midline with interrupted sutures, beginning just back of the urethra and extending upward as far as possible toward the rectum. As they pass over the stumps of the round and broad ligaments they are anchored to them. The excess vaginal mucosa is then excised and the cut edges approximated in the midline. The rectocele and relaxed perineum are repaired in a routine manner to complete the operation.

The rectocele now remains to be repaired. It is well to leave an inch or two of intact vaginal wall for the new posterior wall in the vault of the vagina. To serve as a guide in the dissection, an Allis clamp is placed at that level on the posterior vaginal mucosa and the usual rectocele repair is made. A transverse incision is made at the mucocutaneous junction of the posterior fourchette, and the vaginal wall separated from the rectum up to the Allis clamp serving as a landmark in the vault. The vaginal wall is split up to that point and the levator ani fascia exposed on each side. These structures are approximated in the midline with interrupted medium weight catgut sutures from above down, sometimes in two or more layers to assure adequate pelvic floor support. Likewise, the perineal body structures on each side are approximated in the perineorrhaphy. The excess posterior vaginal wall is excised as a triangle with the apex in the vault, and the edges are brought together with interrupted fine chromic sutures picking up the underlying structures to obliterate "dead space."

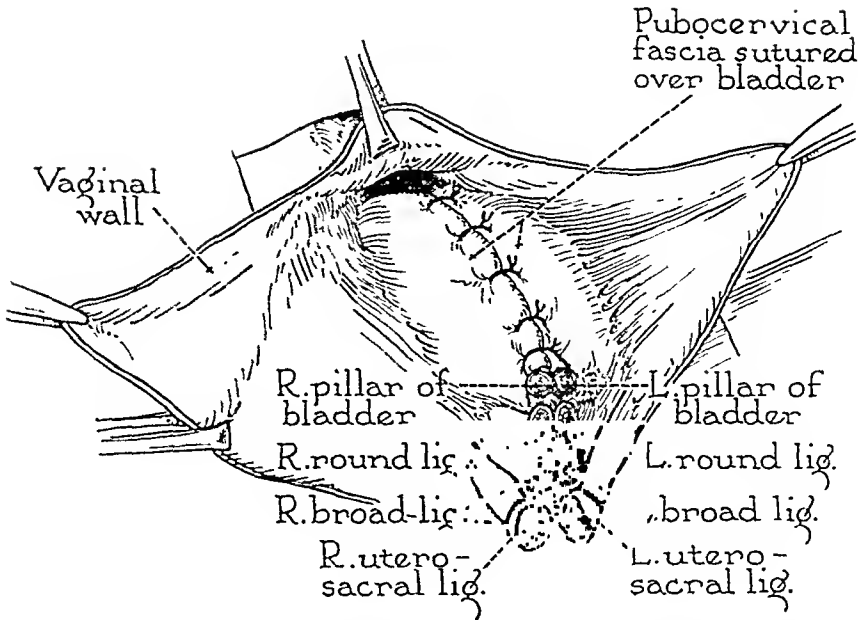


Fig. 4.—The cut edges of pubocervical fascia are approximated in the midline with interrupted chromic catgut sutures after the bladder has been advanced upward. The cut ends of the round and broad ligaments are then sutured together in the midline, and the cut ends of the pubocervical fascia, which include the so-called pillars of the bladder, are anchored to them for support.

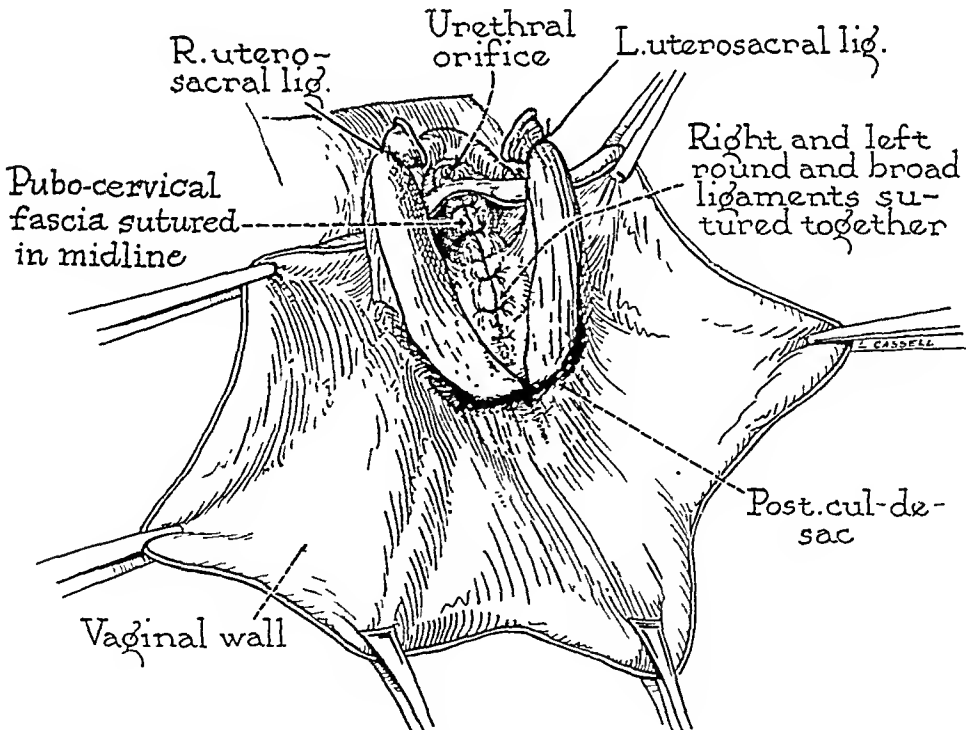


Fig. 5.—The cut ends of the right and left uterosacral ligaments, previously mobilized in part, are now further dissected so that they may be brought forward over the sutured broad and round ligaments and pubocervical fascia to the subpubic arch. They are next sutured to the strong arcuate pubic ligament on each side of the urethra, beneath the mucosa of the introitus, with silk or catgut mattress sutures. As an alternate procedure, the uterosacral ligaments may be placed deep to the pubocervical fascia, in which case the ends of the pillars of the bladder are sutured to them rather than to the stumps of the broad ligaments.

carried out according to the principles of any hernia repair wherein the sacs are obliterated and the fascia and muscle reconstructed. It not only supports the pelvic viscera, but also preserves the natural function of the vagina. In the hands of the authors the method herein described has proved very effectual to date; however, the ultimate end results of this procedure can be evaluated only as a larger series of cases is treated in this manner and more time is allowed to properly evaluate their late postoperative findings.

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### Discussion

DR. JOSEPH L. BAER.—Concerning the substance of the article, there are a few comments which should be registered. Dr. Kooistra says that it is generally agreed that the numerous operations commonly used for the repair of third degree pelvic herniation, popularly called uterine prolapse, are not completely satisfactory, since recurrence of the herniation is common, and because an unsatisfactory vagina is frequently the end result. If his conclusions are predicated on that premise then, of course, one must take issue. In my own experience, the end result has not been commonly unsatisfactory. On the contrary, with the procedures which I shall outline rather briefly recurrence of cystocele or vaginal prolapse is so unusual that I have no present recollection of any such, and the foreshortening of the vagina from the standpoint of marital relations has yet to come to my notice.

## Complications and Postoperative Care

The vagina is packed loosely at the time of operation to prevent adhesions between the anterior and posterior suture lines; the pack is removed forty-eight hours postoperatively. A Foley bag catheter is inserted before the patient leaves the operating room to determine the amount and character of urine, and to rule out operative trauma to the urinary tract, as well as to drain the bladder.

Until recently a majority of the patients operated upon complained of dysuria and frequency as a result of urinary infections which commonly developed. This complication has been minimized by leaving the Foley retention catheter in place for five to seven days to provide constant drainage. It is then removed and the patient requested to void at least once every six hours; if unable to void, she is catheterized. After voiding the patient is catheterized to note the amount of residual urine; this is continued until one ounce or less of urine is obtained on three consecutive catheterizations. In cases of urinary infection, small doses of oral sulfadiazine are given, which usually effect a prompt cure.

Hematomas or infected hematomas constitute the next most frequent complication. These usually rupture spontaneously, some as late as ten days postoperatively. They may be discovered by palpation under sterile precautions, and, if found, they are opened with a blunt instrument either under hypodermic narcosis or light intravenous pentothal anesthesia. Secondary hemorrhages which required treatment were also occasionally encountered. These patients were returned to the operating room and under intravenous pentothal anesthesia the bleeding points were ligated. In each case the bleeding arose from the posterior vaginal mucosa. Improved surgical technique based on the principle of approximation rather than strangulation of tissues plus better hemostasis through careful ligation of all individual bleeders has today practically overcome the problems of hematoma formation and secondary hemorrhage.

Pelvic infections or wound infections not related to hematoma formation occur relatively rarely. In our series of over 100 cases, only three such infections were encountered, and they were all readily controlled by the use of sulfonamides and more recently parenteral penicillin.

## Results

An accurate evaluation of the end results of the operation herewith described is limited by the fact that this technique has been employed for only the past four years. The publication of this paper was postponed for one year in order to better evaluate the end results which at this time are very gratifying. Up-to-date studies of one hundred and four cases, ranging from eighteen months to four years postoperatively, show only two failures: one recurrent cystocele and one postoperative enterocele. In no case was vaginal function unsatisfactory postoperatively. There were no resultant vaginal fistulas. No cases of thrombophlebitis, pulmonary embolism, or postoperative pneumonia were encountered. There were no deaths in this series.

## Summary

Third degree herniation of the pelvic viscera constitutes a disabling disease entity for which many procedures of operative repair have been devised, none of which to date have proved completely satisfactory. Herewith is presented a new modification of repair following vaginal hysterectomy which utilizes an advancement of the uterosacral ligaments to the pubic arch. It is

Then I do a vaginal hysterectomy. When I am through I have mobilized the mucous membrane of the vagina, the peritoneum anteriorly, the peritoneum posteriorly. The next step is to take care of the bladder. We start plicating the tissues along the urethra and along the bladder itself. When we are ready to support the structures, the peritoneum is picked up first and then the round ligament which is followed to the suprapubic or urogenital diaphragm, depending upon how broad the arch of the pubis is. In closing the peritoneal cavity, the round ligament, the cardinal ligament, and the peritoneum are united, which finally brings peritoneum to peritoneum. Dr. Kooistra sewed the two round ligaments; I tie them. I tie the two uterosacrals and remove the redundant mucous membrane and bring the two edges together with perineorrhaphy to finish the operation.

Since using this technique we have had no recurrence of cystocele, no peritonitis, no embolic phenomena.

DR. KOOISTRA (Closing).—Dr. Baer takes exception to my use of the word "common." When the literature shows from 4 to 30 per cent recurrences, in one form or another, I think the use of the term "common" is permissible. I agree with him that the reconstruction of the fascial plane is indeed important. I believe that the uterosacral ligament is not as much of a definite ligament as it has been considered in the past; in the anatomic laboratory we find that this ligament thins out pretty much as you proceed backward toward the sacrum and when you draw it forward, you are not only pulling forward one individual ligament but part of the cardinal ligament and all of the endopelvic fascial structures alongside of it as well. We use the uterosacral ligaments in the repair of our second and first degree prolapses; in those cases where the ligaments are long enough we pull them forward to the pubic arch; when we cannot do that, then we use the procedure described by Dr. Baer.

I find Dr. Kanter's technique very interesting. I think he obtains about the same results that we do. The only difference in the end results is that in his operation round ligaments are sutured to the ligamentous attachments on the pubis, whereas we attach them to the broad ligament and approximate all these structures together in the midline.

Vaginal herniation of the pelvic viscera is in general dependent upon damage to the fascial structures which support those viscera. It was learned that muscle approximation and utilization of the muscles for the correction of herniation of any kind was futile; that good results are to be obtained only and if fascia is included. Here we are dealing with the endopelvic fascia which extends from the symphysis and descending rami of the pubis to the cervix, laterally to the pelvic wall and posteriorly to the junction of the second and third sacral vertebrae. Parts of this fascial plane are the cardinal ligaments and the uterosacral ligaments. A break-through of the bladder must be corrected by the reconstruction of that fascial plane.

The two general conditions which we may find in the elderly woman in whom we have decided to remove the uterus as part of the cure of her procidentia may be either that the supporting structures, which are overstretched, can be brought together very readily transversely, or can be brought together anteroposteriorly. From the standpoint of cure of prolapse it makes very little difference. A good deal of importance has been attached to imbrication of the broad ligaments and cardinal ligaments after removal of the uterus in order to give the bladder and pelvic contents proper support. Yet in the clamp hysterectomy, the uterus is removed in three minutes or less; the clamps are left attached for forty-eight hours. After forty-eight hours with the clamps removed those women subjected to a three-minute hysterectomy have a complete cure. They have no prolapse and no dyspareunia. There was no subsequent prolapse, and no need for having brought the ligaments together in the midline. The Mayo Clinic technique, which has wide popularity, of imbrication of the cardinal ligaments is splendid when those ligaments are adequate and sufficiently elongated so that they can be approximated transversely.

Good results also seem to be obtained by uniting the round ligaments, cardinal ligaments and uterosacral ligaments on one side and then uniting the same three structures on the opposite side with little or no attempt to bring them together in the midline, so long as the peritoneal cavity is closed and the vagina reconstructed.

Dr. Kooistra has offered for consideration a procedure whereby, after midline approximation, the uterosacral ligaments are brought upward and anchored under the rami of the pubis. I see no objections to this. I must confess that I cannot agree with his statement that because these structures are overstretched, they are prone to become thickened. Overstretched and atrophic muscle fibers of the uterosacral ligaments and round ligaments do not hypertrophy. Nevertheless, it is wise to make use of them and their fascial accompaniment in whatever way one chooses.

DR. A. E. KANTER.—I have been using a technique very similar to this for a number of years and I believe it answers the purpose as well as any. I do not say it is better than any other procedure, but it does answer the purpose.

Dr. Kooistra lays a great deal of stress on the uterosacral ligaments and, as Dr. Baer showed, cutting the uterosacrals has very little effect on the uterus. It is not the uterosacral but the cardinal ligaments that keeps the uterus from descending.

I have done this operation on a patient as old as 80 years; it carries with it very little morbid shock, and certainly is very superior to the Le Fort operation. It carries very little morbidity and no mortality if you study the blood chemistry. If the patient has nitrogen retention in the blood stream and the kidneys do not function properly, this operation carries a little more pressure on the uterus than do other procedures, and such a woman may not be able to stand the operation. If the blood chemistry is normal, I have no hesitancy in doing the operation.

The biggest problem is the question of retaining the serviceability of the vagina. In doing this operation; I measure the length of the vagina and determine how long I am going to leave it. The first incision is through the mucous membrane only; a T-incision which is extended upward. I am conscious of the fact that the bladder has prolapsed almost to the tip of the uterus, so I work the mucous membrane down until I see the pillars of the bladder, which I cut across. The bladder is then pushed up and a retractor inserted to hold it in place.

on whom subtotal hysterectomies were performed for myomas, and subsequent pathologic examination revealed the presence of carcinoma originating in the cervix. As a result of this experience we stress the necessity of careful inspection of the cervix before subtotal hysterectomy is performed, with biopsy of all cervical lesions which are even vaguely suspicious of malignancy.

All patients with pathologically proved cancer of the cervix were admitted to a hospital floor separate from the other gynecologic patients. Each received a thorough physical examination, and under those circumstances where the pelvic examination was considered unsatisfactory, it was done under anesthesia. The pelvic findings were divided into the clinical stages as outlined by the League of Nations. In an effort to standardize clinical classification, the same senior members of the permanent staff examined all patients whenever possible.

When it was doubtful as to which stage a given case should be allocated, the earlier one was chosen. Investigations of the genitourinary and gastro-intestinal tracts were carried out in all cases where indicated. Treatment was instituted in every instance while the patient was hospitalized. The value of hospitalization is twofold: first, it assures that the patient carries through with the whole treatment; and second, it affords a better opportunity for the early recognition and prompt treatment of undesirable side effects of radiation.

There were 212 patients handled in the above fashion from 1933 through 1944. The youngest patient was 24 years old, the oldest 83 years of age. Fig. 1 indicates the age range according to decade. The majority of the patients were between 30 and 60 years of age, and were almost equally represented in the fourth, fifth, and sixth decades. Nine patients were under 30 years, representing 4.3 per cent; ten were over 70 years of age. Eighty-six and five-tenths per cent of the patients had borne children; the largest percentage had had two. Thirteen and five-tenths per cent were nulliparous.

Fig. 2 shows the duration of symptoms. Accurate determination as to the duration of those symptoms, which were specifically related to the cancer, was, of course, not always possible. Approximately 74 per cent of the patients had symptoms for six months or less, 38 per cent for three months or less, and 10 per cent had no symptoms. The largest number of patients had symptoms for three months or less.

A definite pathologic diagnosis of adenocarcinoma of the cervix was made in 17 cases, an incidence of 7.9 per cent. It is interesting that in five of these cases a diagnosis of adenocarcinoma of the fundus was made after curettage, and a panhysterectomy and bilateral salpingo-oophorectomy subsequently performed. Pathologic study revealed the carcinoma to be of cervical origin. It has not been our practice to do fractional curettages, and perhaps such a procedure would have helped avoid this error.

There were 12 cases of cancer of the cervical stump. Three of these were discovered immediately after subtotal hysterectomy by pathologic study, one was discovered two months after operation, and the remaining eight cases were found two years or more after hysterectomy. These eight may be considered as true cases of cancer of the cervical stump if we are correct in assuming that the lesion was not present at the time of operation, an incidence of 3.8 per cent. Specifically, three of the eight patients had had a hysterectomy slightly over



## CARCINOMA OF THE CERVIX

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IT IS the purpose of this study to present a statistical analysis of facts concerning all patients with a proved diagnosis of cancer of the cervix uteri treated in this clinic from 1933 through 1944. Although the series is relatively small, this study will afford a base line for future investigation and will give some indication of the success or failure of treatment to date and thereby afford a means of comparison for results of future and hopefully better therapy. In presenting this data, an effort has been made to conform to the rules and pattern of presentation and analysis as outlined by the League of Nations Annual Report of 1935.

All cases of cancer of the cervix and cervical stump microscopically diagnosed as such from 1933 through 1944 have been reported with the following qualifications:

1. All cases of intraepithelial and questionable cancer have been excluded.
2. All patients who, after a definite diagnosis, refused treatment have been excluded.
3. Those patients in whom the cancer was too far advanced to warrant treatment have been included.
4. All patients lost in the follow-up have been counted and assumed dead.

Taking the above qualifications into consideration, it has been possible to report on 212 patients, 115 of whom have been followed for at least five years. This latter group includes all patients seen from the middle of 1933 through 1940.

Of the remaining 97 patients seen from 1941 through 1944, it is possible to report four-, three-, two-, and one-year survival rates from which some indication as to the relative success or failure of therapy in these years as compared with former years can be acquired. This comparison is particularly relevant because of the fact that late in 1939 our dosage and technique of administering x-ray were altered.

The patients have come from four sources. The majority have come from the gynecologic outpatient department, presenting themselves with complaints, many of which were not related specifically to the cervical lesion. It has been our practice to do biopsies on all cervical lesions that are even slightly suspicious of cancer, and a sizable number of our patients with early cancer were found in this fashion. A small number were referred to the clinic with a known diagnosis, either from the other departments in this hospital or from outside physicians. Finally, there was a group of patients found to have cancer after an operative procedure for another condition. There are several cases

two years before the cancer was found; two patients, three years; one patient, five years; one patient, eleven years; and one patient, nineteen years before.

There were two cases of cervical cancer complicated by pregnancy. One was discovered in the third month, the other in the seventh month of gestation. There were two cases in which the cancer was found four and five weeks post partum, presumably present in both during the latter part of the pregnancy.

It is now generally believed that histologic classification is of questionable value in making a prognosis in cervical cancer. In our series there was no apparent correlation between histologic classification and survival rate. Of far greater significance is the clinical classification as outlined above. As is borne out in this study, the prognosis depends in most cases on the stage of the disease when the patient is first seen. If the malignancy has not spread beyond the cervix, that is, a Stage I, the chances for salvage are good, while at the other extreme, Stage IV, with the carcinomatous process invading the bladder or rectum or extending out of the true pelvis, the prognosis is invariably hopeless. Table I shows in detail the number and percentage of cases in each stage. In the 115 cases treated from 1933 through 1940, on whom a five-year salvage rate can be reported, about 25 per cent of the cases were in Stage I, 41 per cent were in Stage II, 24 per cent in Stage III, and 10 per cent in Stage IV. In this group, then, 66 per cent, or two-thirds of the cases, were in Stages I and II. Similarly, in the cases treated from 1940 through 1944, 63 per cent, or approximately two-thirds, were in Stages I and II. In contrast to the figures reported from various city hospitals and free institutions, our series shows a higher percentage of early carcinomas, and consequently our patients were in better physical condition when first seen. The number of patients who had suffered exhausting hemorrhages before admission was small, as was the number who were suffering from severe extragenital disease.

TABLE I. CLASSIFICATION OF PATIENTS INTO CLINICAL STAGES

YEAR	TREATED	LOST	STAGE I		STAGE II		STAGE III		STAGE IV	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
1933-1934	16	1	4	25.0	9	56.0	2	12.5	1	6.3
1935	16	0	5	31.1	5	31.1	5	31.1	1	6.3
1936	15	3	3	20.0	7	46.6	4	26.6	1	6.7
1937	18	0	3	16.6	8	44.4	5	27.8	2	11.1
1938	18	1	4	22.1	6	33.3	4	22.1	4	22.1
1939	18	1	8	44.5	7	38.8	2	11.5	1	5.6
1940	14	0	2	14.5	5	35.8	5	35.8	2	14.5
Total	115	6	29	25.1	47	40.8	27	23.4	12	10.4
1941	28	0	11	39.5	10	35.4	6	21.2	1	3.7
1942	20	0	7	35.0	6	30.0	6	30.0	1	5.0
1943	25	0	6	24.0	7	28.1	10	40.0	2	8.0
1944	24	0	4	16.6	10	41.5	9	37.5	1	4.1
Total	97	0	28	28.9	33	34.0	31	32.0	5	5.2

As stated above, all of our patients were hospitalized during the initial stages of therapy, at least. Of the 212 patients in the series, 169, or approximately 80 per cent, were treated with x-ray and radium. Because the x-ray is utilized to combat the parametrial infiltration which will eventually cause the patient's death if unchecked, it was given first in most instances. Further advantages of this regimen of treatment are that the x-ray aids in clearing up infection and reduces the size of the tumor, thereby making the insertion of radium easier and more effective. Since 1940, the x-ray radiation factors have been appreciably changed: 250 kilovolts have been substituted for 200, fil-

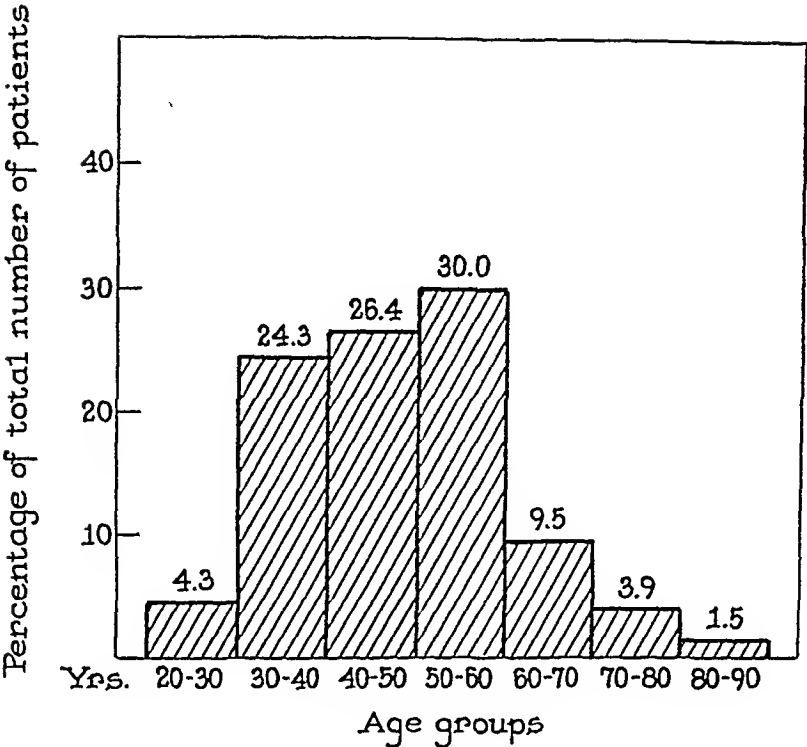


Fig. 1.—Age distribution in decades.

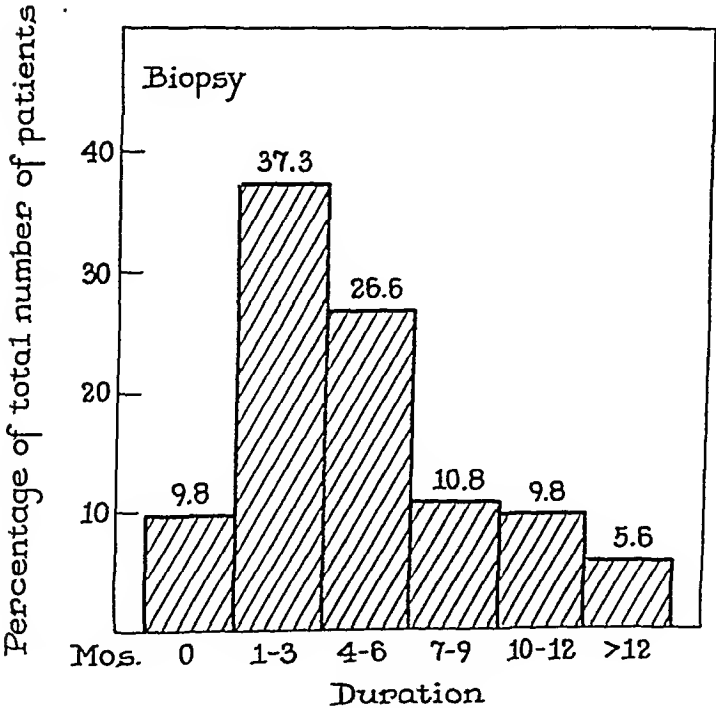


Fig. 2.—Duration of symptoms.

TABLE III. A COMPARISON OF LATE RADIATION REACTIONS OCCURRING BEFORE AND AFTER  
1940—115 PATIENTS BEFORE, 97 PATIENTS AFTER

REACTION	1934-1940	1941-1944
Bladder (cystitis)	9	4
Rectum (proctitis)	6	6
	4	0
Skin (telangiectasis, ulceration and pigmentation)	1	1
	2	3
Fistula formation		
Vesicovaginal	3	1
Rectovaginal	1	1
Sigmoidvaginal	1	
Obstruction of the ureters	1	1 (partial)
Fracture of the femur	2	
	<u>30</u>	<u>17</u>

To date there have been 47 cases of late radiation reactions, an incidence of 22.1 per cent. These are summarized in Table III. The most common late complication in our series has been bladder injury. Dean<sup>2</sup> has accurately described late ulcerative lesions occurring in the bladder following irradiation of the uterus. He recognizes three types of lesions: a primary erythema occurring within twenty-four hours after treatment and being a nonspecific reaction to local irritation; secondary erythema appearing within a month after treatment and being a specific reaction to irradiation, probably due to temporary vasodilatation; and a tertiary reaction consisting of obliterative endarteritis with sloughing and ulceration of the tissues, rarely appearing earlier than a year, sometimes as late as ten years after treatment. Everett<sup>3</sup> has reported that the presence of lesions of the upper urinary tract before treatment in patients with cancer of the cervix is of grave prognostic significance, and that approximately 50 per cent of these patients, after treatment, show evidence of some obstructive lesions involving the lower ureters with resulting dilatation of the kidney pelvis and ureter. Everett states that in only about 15 per cent of these patients are the lesions of sufficient severity to be of clinical importance, but that this incidence is sufficiently high to render routine urologic study a justifiable and important part of the follow-up. In our study there were nine cases between 1934 and 1940 and four from 1941 through 1944, all manifested by symptoms of chronic cystitis with or without hematuria. Unfortunately, no careful urologic study was made in these cases. Numerous instances of mild cystitis occurred during treatment, but symptoms usually disappeared within a month or two. In only one patient apparently cured of cancer did obstruction of the ureters occur necessitating transplantation.

Injury to the rectum resulting in proctitis was the second most frequent complication. Radiation effects upon the rectal mucous membrane result in definite clinical signs which vary in proportion to the intensity of radiation.<sup>4</sup> A number of patients had a mild diarrhea during the latter part of therapy. The symptoms varied from watery diarrhea with two to four stools daily to severe abdominal pain, tenesmus, and frequent stools. With the improved technique, the incidence of this early complication has been appreciably reduced. Other gastrointestinal symptoms of nausea, vomiting, and anorexia have been combated with the use of 50 mg. of pyridoxine daily. We can make no definite statement, at this time, as to the therapeutic effectiveness of this drug. There have been 12 cases of late protracted proctitis, manifested by diarrhea and tenesmus. In these instances, ischemia with fibrosis and scarring of the rectum has probably occurred. Proctoscopy was carried out where there was any question of tumor recurrence in the rectum.

ters" of  $\frac{1}{2}$  mm. copper and 1 mm. aluminum for the Thorius filter formerly used, and the skin target distance has been increased from 50 to 70 centimeters. For the greater distance a longer irradiation time is necessary to deliver a specified amount of radiation to the skin, but when this has been done the depth dose has been proportionately increased. It is now our practice to give an average of 2,200 r's in air to each of six pelvic ports and to an intravaginal port. In those cases where the intertrochanteric distance was too great to justify the use of the lateral ports because the depth dose would have been negligible, two anterior and two posterior ports alone were used. The anterior ports measured 11 by 14 cm., the posterior 12 by 15, and the lateral 10 by 14 cm. The use of the intravaginal port, started in 1940, has aided considerably in reducing the size of the tumor and clearing up infection before the insertion of radium. The massive dose technique has been replaced by the fractionated or divided dose method, for, as shown by Arneson,<sup>1</sup> the total amount of roentgen radiation delivered to the parametrium in the divided dose technique is much greater than that given by the massive dose method. It is now our practice to administer 200 r's to each of two portals daily in place of the 500 r's formerly given. Generally, it can be said that the changes in the x-ray factors were made in an effort to administer greater depth doses with fewer secondary reactions.

In most cases the radium was given one month after the last x-ray treatment. The advantages gained in waiting this period of time are that the maximum shrinkage of the tumor is allowed to occur, and the patients seem to tolerate the radium better with fewer side effects. The average intracavitary dose has been 3,600 mg. hr., in the form of one 100 mg. and one 50 mg. capsule of radium filtered with aluminum and monel metal, in rubber tubing. We have used interstitial  $12 \frac{1}{2}$  mg. needles in selected cases.

Twenty-four patients received x-ray alone. This group for the most part represented advanced cases in which radium could not be used because of the presence of severe infection or hemorrhage or would have been of little value in prolonging the patient's life. Two Wertheim operations were performed, one being followed by x-ray. Panhysterectomy and bilateral salpingo-oöphorectomy followed by x-ray were performed on five patients, and radium followed by panhysterectomy in one instance. All of these six surgically treated patients had adenocarcinoma of the cervix, and in the five cases treated with operation first, a diagnosis of adenocarcinoma of the corpus uteri had previously been made. The remaining cases were treated as follows: radium alone, two; amputation, two; amputation and x-ray, three. There were four cases not treated because the disease was too far advanced. In summary, as is shown in Table III, all but 17 of our patients were treated with some combination of x-ray and radium, or x-ray alone, or by radium alone.

TABLE II. CLASSIFICATION OF PATIENTS ACCORDING TO TREATMENT USED 1933-1944

X-ray and radium	169
X-ray	24
Wertheim operation	1
Wertheim and x-ray	1
Panhysterectomy, bilateral salpingo-oöphorectomy and x-ray	5
Radium and panhysterectomy	1
Radium	2
Amputation of the cervix	2
Amputation and x-ray	3
Not treated	4
Total	212

mine in the largest percentage of cases the actual cause of death, due to the fact that most died at home or in homes for terminal care, we have assumed that all died of cancer. Forty-nine patients, or 42.5 per cent, survived for at least five years. Of these 49 patients, 44 were classified as Stages I or II when first seen; specifically, 23 were Stage I and 21 Stage II. Of this group of 115 patients, 51, or 44.3 per cent, survived four years, and 59, or 51.4 per cent, at least three years. The observation that there is a small difference between four- and five-year survival rates, and only a slightly greater difference between three and five years, indicates that if a patient survives three years, her prognosis is certainly favorable. As yet it is impossible to make any conclusive statements about late recurrences. There were 76 of these 115 patients who were originally classified as Stage I or Stage II, and of these 44, or 58 per cent, survived at least five years and represent 90 per cent of the patients who survived for the five-year period. These figures indicate that a patient classified as having Stage I or Stage II cancer of the cervix had almost a 60 per cent chance of living five years, whereas a classification of Stage III or Stage IV carries a hopeless prognosis beyond this period.

It is of some interest to study the yearly survival rates of those 97 patients seen after 1940, when radiation factors were changed, as outlined above. It has been pointed out that the percentages of cases in Stages I and II remained relatively constant through the years, and thus this group is comparable to that seen before 1941. There seems to be a slight improvement in one-year survival rates from 1941 through 1944, as compared with the period from 1938 to 1940, although none over 1934 to 1937 results.

TABLE IV. RESULTS

YEAR	TREATED	LOST	PERCENTAGE ALIVE AFTER—YEARS									
			1	2	3	4	5	6	7	8	9	10
1933-1934	16	1	100.0	100.0	68.5	62.5	62.5	56.5	56.5	50.0	50.0	43.8
1935	16	0	75.0	56.5	56.5	56.5	50.0	50.0	50.0	43.8	43.8	
1936	15	3	86.5	60.0	40.0	33.3	26.8	26.8	20.0	20.0		
1937	18	0	83.5	72.1	51.5	51.5	51.5	51.5	50.0			
1938	18	1	66.8	38.9	33.3	33.3	33.3	33.3				
1939	18	1	66.8	50.0	44.5	38.9	38.9	33.3				
1940	14	0	64.5	64.5	57.0	28.3	28.3					
Total	115	6			51.4	44.3	42.5					
1941	28	0	86.1	57.0	46.5	35.4						
1942	20	0	65.0	45.0	45.0							
1943	25	0	80.0	60.0								
1944	24	0	87.5									
Total	97	0										

Our results are comparable to those in recent reports from other clinics. It is to be noted that unless the percentages of early cases in various series are approximately the same, end results expressed in survival rates are not comparable. Smith and Dresser<sup>7</sup> report a 38 per cent salvage rate from 1929 through 1933, and a 43 per cent rate from 1934 to 1938. McLennan<sup>6</sup> reports an over-all relative rate of 26.4 per cent. Garcia and Schlosser<sup>7</sup> report a five-year survival rate of 28 per cent. It is to be noted that two-thirds of the latter authors' series were classified as Stages III and IV. Healy and Twombly,<sup>8</sup> using about the same technique at the Memorial Hospital as outlined above, report a 35.4 per cent survival rate. The combined international figures, as reported by the League of Nations, show a relative rate on 10,970 patients of 26.7 per cent.

Skin reactions consist of an early epidermitis which expresses itself as a moist denuded area caused by a complete loss of the superficial layers of the epidermis.<sup>4</sup> Such early reactions have not complicated our cases, as dosages sufficient to produce them are not possible if more serious injuries to the bladder and intestines are to be avoided. Late skin changes consist of telangiectasis, atrophy, pigmentation, and, in extreme cases, ulceration. There were seven serious skin reactions between 1934 and 1940, and four between 1940 and 1944. Specifically, there were two cases of ulceration, four of telangiectasis, and five of severe pigmentation.

Seven cases of fistulas occurred. In these, growth of the tumor with ulceration through the bladder or rectum was probably the main etiologic factor, rather than the radiation. There were three instances of vesicovaginal fistula up to 1940 and one case after that time. Rectovaginal fistula developed in one patient seen before, and one seen after 1940. One instance of sigmoid-vaginal fistula developed.

Two patients experienced fracture of the femur, presumably as a result of a sclerosing osteitis from the radiation.

It has been said that infection during the course of irradiation is by far the most important complication associated with radiotherapy of cancer of the cervix,<sup>4</sup> the 2 per cent mortality charged against this procedure being due almost entirely to the activation of hemolytic streptococci by the radiation. Furthermore, it is generally believed that the presence of infection makes the tumor more radioresistant. Occasionally pelvic infections, particularly those resulting from streptococci, have made it necessary to diminish the quantities of x-ray given in the individual treatment and to prolong the time over which the therapy is given. Usually, however, it has been possible to continue treatment in such patients despite considerable febrile reaction. Several cases of early pyometria resulting from occlusion of the cervical canal have occurred in this series, as well as several cases of late pyometria and late infectious parametritis. Whereas a complete study of morbidity, duration of hospital stay, and the effects of the intravaginal port and chemotherapy on infection complicating radiation will be reported at a later date, certain general trends may be described; namely, the incidence of early febrile reactions has been diminishing, and the severity of such reactions has been markedly reduced since the advent of chemotherapy.

It is doubtful if this summary represents all the late reactions that actually occurred, for many of our cases are sent to homes for terminal care as soon as it is evident that the prognosis is hopeless, and it has been impossible for these overcrowded institutions to provide us with complete clinical abstracts.

*Follow-up.*—All the patients after discharge were followed in a special radiation clinic and seen as frequently as indicated, never at an interval greater than a year. With the help of an efficient social service department, we have been able to follow to date 206, or approximately 97 per cent, of the 212 patients in this series. The whereabouts and physical state of the remaining six patients at the moment are not known. It is to be noted that only with a great deal of effort and time has it been possible to trace and contact certain patients. The same senior member of the staff, who sees these patients on admission and advises treatment, has charge of the radiation clinic, and when possible he personally sees them all. In this work he has been assisted by various members of the house staff.

### Results

Survival rates are summarized in Table IV. There were 115 patients followed for at least five years. Because it has been impossible for us to deter-

Of the total of 212 cases, 65 per cent were classed as Stage I or Stage II and 35 per cent as Stage III or Stage IV.

Of the 115 patients seen from 1933 through 1940, 49, or 42.5 per cent, survived for five years or more.

The four-, three-, two-, and one-year survival rates for the 97 patients seen from 1941 through 1944 are not appreciably different from the rates over the first period, i.e., from 1933 through 1940, despite the fact that in 1940 radiation factors and technique were altered.

There were 47 cases of late radiation reactions in the total group of 212 patients, an incidence of 22.1 per cent. There were about twice as many reactions in those patients treated before 1940 as in those treated after 1940. This reduction in radiation complications we attribute to improved technique in radiation therapy.

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Certain general statements can be made as a result of this study. In the first place there was no relation between age and survival rate; that is, the younger patients did not on the average live a shorter time than did the older ones. There was no relation between parity and survival rate or histologic classification and survival rate.

The largest percentage of our patients had symptoms less than three months. This is not remarkable if we take into consideration the fact that two-thirds of our patients had relatively early cancer of the cervix, that is, had lesions classified as Stage I or Stage II. It is to be noted that a relatively large group, approximately 10 per cent, had no symptoms that could be explained by the presence of the cancer when it was discovered. It is in these patients that the routine biopsy of cervical lesions not obviously malignant was so important in establishing the diagnosis. Certainly the value of careful inspection of the cervix in all patients and the free use of the biopsy cannot be over-emphasized, because the patient with an early carcinoma has about a 60 per cent chance of living five years, while the woman with an advanced lesion has practically no chance. Because progress in treatment is slow, great efforts must be made to effect earlier diagnoses, for in this way can we definitely improve end results. This study has shown that among our patients prognosis depends almost entirely on the stage of the disease at the start of treatment.

The relatively high incidence of 3.8 per cent of cancer of the cervical stump in our series of 214 cases of cancer of the cervix raises the argument of the value of total versus subtotal hysterectomy. Some authors feel that there is no justification for leaving a nonfunctioning cervix in place in those cases where it could be removed without appreciably lengthening the procedure or making it more difficult. Others are of the opinion that total hysterectomy results in a higher morbidity, shortening of the vagina, and even fistula formation in some instances, and, therefore, should be reserved for those cases where the cervix is definitely diseased. It can be said that in every instance where the cervix is diseased and a total hysterectomy can be performed safely, such a procedure should be undertaken. If for any reason an unhealthy cervix is left in place, it should be treated postoperatively.

The use of the higher voltage with the divided dose technique, aluminum filtration and intravaginal port, although not resulting in any demonstrable trend toward higher survival rates, has been accompanied by a reduction in the incidence of late radiation reactions to about half, although it is too early to make a definite statement in this regard. In fact, Healy and Twombly<sup>8</sup> report a higher instance of skin reactions and intestinal disturbances in cases treated with the divided dose method than in those treated with the massive dose technique. Later it will be possible adequately to evaluate the worth of the intravaginal port and the use of chemotherapy in reducing the incidence of infection and shortening the period of hospitalization. Because of the higher incidence of infection and the worse prognosis in patients from whose vaginal hemolytic streptococci can be cultured, prophylactic chemotherapy should be instituted in all cases where the hemolytic streptococci has been isolated on routine culture. Our general impression at this time is that a reduction in both morbidity and duration of hospitalization is being achieved by such means.

### Summary

A statistical analysis of 212 patients with cancer of the cervix has been presented.

TABLE I. PRENATAL CARE IN SIXTY-FOUR TOXEMIAS

NO. OF VISITS	COOK COUNTY HOSPITAL	CHICAGO BOARD OF HEALTH	CHICAGO MATERNITY CENTER	OTHERS	PRIVATE M.D.	NO RECORD	NO PRENATAL CARE
0						4	22
1	9	3		1 (Chicago Lying-In)			
2	5	2	3	1 (Reese)	2		
3	3	1	1	1 (Michael Reese)			
4	2	1					
5	1	1					
6							
7	1						
8							
9							
10	1						
Total	22	8	4	2	2	4	22

TABLE II. AGES IN SIXTY-FOUR TOXEMIAS

16 to 20 years, inclusive	7
21 to 30 years, inclusive	29
31 to 40 years, inclusive	22
41 to 46 years, inclusive	6
Total	64

The parity (Table III) ranged from para 0 to para xviii. Thirty-five patients were para iii or less, and twenty-nine were para iv or more. The question of the advisability of bags in para 0's will be analyzed later.

TABLE III. PARITY IN SIXTY-FOUR TOXEMIAS

PARITY	PATIENTS
0	9
i	9
ii	10
iii	7
iv	5
v	8
vi	3
vii	3
viii	3
ix	1
x	1
xi	2
xii	2
xviii	1
Total	64

Two patients were under 24 weeks' gestation (Table IV), nine were between 25 and 28 weeks, seventeen were between 29 and 32 weeks, and the remaining thirty-six patients were 33 weeks or more.

TABLE IV. PERIOD OF GESTATION; TOXEMIAS

WEEKS	LESS THAN 24 WEEKS	25-28	29-32	33-36	37-40	64 Total
No of patients	2	9	17	26	10	

Ten of these patients had one or more eclamptic convulsions (Table V) on admission to the hospital. Seventeen had systolic pressures of *over* 200 mm. of mercury, and a mean diastolic of 130 mm. The thirty-seven remaining patients had a mean systolic pressure of 175 mm. and a mean diastolic pressure of 116 mm.

## THE VOORHEES BAG\*

### An Analysis of Its Use in 164 Cases

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RECENTLY, an increasing number of competent obstetricians have gone on record as being opposed to the use of the hydrostatic bag in the conduct of labor. Williamson,<sup>1</sup> reporting 162 cases of placenta previa in which the hydrostatic bag was used in 51 cases, concludes that it is seldom the method of choice. Watson, in the discussion of Williamson's paper, says, "I believe the hydrostatic bag belongs to a past era in obstetrics." This is an opinion in which Cosgrove concurs. Before this Society at the January meeting, Davis criticized the use of bags in bleeding patients.

In an effort to evaluate the merits of the Voorhees bag and, if possible, to determine whether or not it has a place in modern obstetrics, this study was undertaken. The Cook County Hospital records were reviewed for a seven-year period, from 1938 to 1944, inclusive. During this time, 164 bags were used in a variety of situations. Hillis and Benensohn<sup>2</sup> state in a paper on "Fetal Mortality," that 196 hydrostatic bags were used at the Cook County Hospital in the four-year period from 1933 to 1936, inclusive. In a seven-year period, we have found only 164, so apparently the staff is making use of this method of delivery less often than formerly.

The classical indications for the use of bags as given in most obstetric textbooks are three: (1) to induce labor (usually in toxemia), (2) to prevent bleeding (placenta previa), and (3) to aid in dilatation of the cervix and prevent prolapse of the cord and small parts in abnormal presentations (transverse, breech, footlings, face, etc.).

So that an orderly presentation of the findings may be given, these 164 bag introductions have been classified according to indications. There are 64 toxemias; 82 bleeders (62 placenta previa, 20 abruptio placenta), and 18 miscellaneous indications. These are reported in three groups.

#### Toxemias

Twenty-two of the toxemias (Table I) had no prenatal care, and thirteen had attended a clinic on only one occasion, at which time they were sent directly into the hospital. Thirteen had made two visits for prenatal care, five had made three, and two had been to a clinic on four occasions. Two patients had been to a clinic five times, and one had been to the Cook County Hospital Clinic seven times and one ten times. These last two were the only patients in the series who may be said to have had adequate prenatal care.

The ages (Table II) ranged from 16 to 46 years, seven being from 16 to 20 years of age, twenty-nine being from 21 to 30 years of age, twenty-two from 31 to 40 years of age, and six from 41 to 46 years, inclusive.

\*Read before the Chicago Gynecological Society, April 19, 1946.

TABLE VI. ECLAMPSIA—TEN PATIENTS

AGE (YEARS)	PARA GRAVIDA	ADMISSION BLOOD PRES- SURE	PRE- NATAL VISITS	CONVULSIONS BEFORE   AFTER ADMISSION	PERIOD OF GESTA- TION (WEEKS)	FETAL HEART TONES AT ADMISSION	MEDICAL INDUC- TION	LENGTH LABOR	BABY	MORBID- ITY	HOME (DAY)	DIS- CHARGE BLOOD PRES- SURE
*1. 25	iv v	240 120	0	2   1	24	0	2	12 hr.	Mac. S.B.	102 I.P.	9	122 80
2. 32	iv v	250 120	0	2   0	32	+	0	10 hr. 50 min.	L.B.	0	12	150 90
3. 16	0 i	190 130	0	1   1	32	0	0	15 hr. 20 min.	S.B.	101 I.P.	10	164 90
4. 38	ix xii	218 148	0	1   0	32	0	3	18 hr. 20 min.	Mac. S.B.	0	12	120 100
5. 37	iv v	204 110	2	2   1	28	+	2	12 hr.	L.B.	0	11	No Rec.
†6. 29	vi viii	240 146	0	2   3	28	0	2	1 hr. 20 min.	Mac. S.B.	102 P.P.	8	220 100
7. 32	vii viii	230 160	0	2   1	28	+	0	3 hr. 36 min.	L.B.	0	9	130 90
‡8. 19	0 i	180 140	0	1   0	36	+	2	15 hr.	S.B.	0	12	No Rec.
9. 23	0 ii	170 110	10	2   1	26	0	2	24 hr.	Mac. S.B.	101 P.P.	8	140 90
10. 31	vi vii	190 120	2	1   1	36	+	0	12 hr. 15 min.	S.B.	0	12	126 80

\*Failed bag.

†Home on release.

‡Bag removed; Willet forceps to head.

TABLE V. TONEMIAS

10	Eclampsics with one or more convulsion
17	Had systolic pressure of over 200 mm., and a mean diastolic of 130 mm.
37	Had a mean systolic pressure of 175 mm., and a mean diastolic of 116 mm.
64	Total

Seven of those who had convulsions (Table VI) had had no prenatal care, and only one had had adequate prenatal care, which was not effective in her case as she had an acutely fulminating type of toxemia with symptoms of only four days' duration. All were treated from one to nine days conservatively (hypertonic fluids and sedation) before a bag was used. In five, fetal heart sounds were absent on admission; of the five patients in whom fetal heart sounds were present, two were para iv, one was a para vi, one a para vii, and one a para 0.

In six patients, medical induction had failed. Seven bags were intraovular, and there were extraovular.

The first history (Table VI) is of a "failed bag." This patient was a para iv gravida v with a 24 weeks' gestation and absent fetal heart sounds. A 7 cm. extraovular bag was in place for forty-four hours without labor being established. It was then removed and the membranes were ruptured. Quinine was given to the patient and she delivered a macerated stillborn baby twelve hours later. She had a temperature of 102° F. intra partum, but recovered promptly, and went home on the ninth postpartum day.

There are three para 0's in these 10 cases of eclampsia, but it will be noted that two of them had absent fetal sounds on admission. Of the third (Case 8, Table VI), nothing can be said in favor of the management. A 19-year-old, para 0, grav. i of 36 weeks' gestation, had one convulsion before admission, and came into Cook County Hospital with good heart sounds. A nine cm. extraovular bag was placed, and, after 11 hours and 10 minutes, it was taken out. The patient was in early labor, and the cervix was 4 cm. dilated. The reason for taking the bag out is not clear. A Willet forceps was applied to the infant's scalp, and shortly thereafter, fetal sounds were not heard. The cervix was completely dilated after fifteen hours and a craniotomy done. It would seem that this patient was a good candidate for a cesarean section, and that the choice of the bag was ill advised.

In all other cases, including Case 10 in which a stillbirth resulted, delivery from below was a reasonable procedure since all were either multiparous patients or fetal sounds were absent. In the tenth case, the patient was a 31-year-old para vi, gravida vii, who had one convulsion before admission, and one after coming to the hospital. She had a viable baby and heart sounds were present. A 10 cm. intraovular bag was inserted, but labor did not start for fifteen hours, and heart sounds were lost before the bag was expelled at the end of thirty hours. A 5 lb., 7 oz. stillborn baby was delivered spontaneously.

In 39 instances, extraovular bags were used, and in 25, intraovular bags were placed. The selection of cases followed no pattern as to indications. Some members of the staff are reluctant to sanction the rupture of the membranes for fear of infection, or prolapse of the cord. Others consider that the advantage in time gained with intraovular bags justifies the risk. Our findings in this group of cases seem to bear out the latter view.

In thirty-nine patients with extraovular bags, as shown in Table VII, twelve began labor promptly, and the remaining twenty-seven established labor in from one to thirty-six hours. The average length of labor for this entire group was fifteen hours and thirty minutes. In twenty-five patients with intraovular bags, fifteen patients established labor within thirty minutes, and the remaining ten

In analyzing the fetal mortality (Table VIII), we find that fetal heart tones were absent before the bag was introduced in nineteen instances, and in eight instances they were lost between the introduction of the bag and delivery. Thirty-eight babies were born alive, but four of these died in the first forty-eight hours of the neonatal period. Sixty-five babies are reported, because there is one set of twins in the series.

TABLE VIII. INFANTS OF SIXTY-FOUR MOTHERS WITH TOXEMIA

Fetal heart tones absent before bag inserted	19
Fetal heart tones lost after bag inserted (intrapartum)	8
Neonatal deaths (one twin)	4
Live births (one twin)	34
Total	65

### Intrapartum Fetal Deaths

There were eight intrapartum deaths, two of which were reported with the maternal deaths, and two with the eclamptics. Histories of the remaining four are as follows:

CASE 1.—B. R., aged 21 years, thirty-four weeks' gestation, para 0, gravida i, with a blood pressure of 260/170, and four plus albumin. No prenatal care. The patient had a temperature of 101° F., and the membranes had been ruptured fifty-six hours on admission. Heart sounds were present. The cervix was 3 cm. dilated, and the patient complained of mild pains, but no contractions were observed. A 9 cm. intraovular bag was placed in the cervix, and twenty hours later a stillborn infant, weighing 4 lb., 15 oz., was delivered spontaneously. The mother had a fever of 102° F. for four days. She was discharged on her fifteenth postpartum day with a blood pressure of 165/95.

CASE 2.—A. H., aged 28 years, twenty-six weeks' gestation, para 0, gravida i, with a blood pressure of 160/110. No prenatal care. This patient had hemiplegia and projectile vomiting on admission. There was a marked hematuria, and only 400 c.c. output on the first hospital day. The patient was treated medically for eight days, and on the ninth day a 8 cm. extraovular bag was introduced which was in place eighteen hours. After a five-hour labor the bag was expelled, the membranes ruptured spontaneously, and the cord prolapsed. The cervix was completely dilated, and the infant delivered promptly, but a 2 lb. stillborn infant was obtained.

CASE 3.—L. M., aged 22 years, twenty-six weeks' gestation, para i, gravida ii, with a blood pressure of 226/154, and edema and four plus albumin. Two prenatal visits. The patient had a retinal detachment on admission. Conservative treatment was used for two days, after which an 8 cm. intraovular bag was placed. The fetal heart tones disappeared after two hours, and at the end of five hours and thirty minutes, a stillborn infant, weighing 1½ lb., was delivered spontaneously. The patient signed a release and went home on her tenth postpartum day.

CASE 4.—E. C., aged 41 years, thirty-four weeks' gestation, para vii, gravida viii, with a blood pressure of 170/110, edema, blurred vision, and four plus albumin. Two prenatal visits. Two attempts at medical induction failed. On her third hospital day a 6 cm. extraovular bag was placed, and after two hours and forty-five minutes the bag was expelled. The membranes ruptured spontaneously, and the cord prolapsed. The patient was placed in Trendelenburg position, and a 10 cm. bag was introduced, but the fetal sounds were lost. After a total labor of seven hours and fifty-five minutes, a stillborn infant weighing 5 lb., 13 oz., was delivered spontaneously. The patient was afebrile, and went home on the eighth postpartum day. A larger intraovular bag should have been used.

TABLE VII. BAGS USED IN SIXTY-FOUR TOXEMIAS

EXTRAOVULAR BAGS			INTRAOVULAR BAGS		
NUMBER OF PATIENTS	LABOR ESTABLISHED		NUMBER OF PATIENTS	LABOR ESTABLISHED	
	HOURS	MINUTES		HOURS	MINUTES
12		30	15		30
3	1		2	1	
3	3		1	3	
2	4		3	6	
4	5		1	8	
3	7		1	14	
4	8		1	24	
2	10		1	30	
2	12				
1	15				
1	20				
1	36				
1	Failed—in place 44 hours (No. 1 on Table VI)				
Average length of labor—15 hr., 30 min.			Average length of labor—8 hr., 36 min.		

in from one to thirty hours. The average length of labor in this group was eight hours and thirty-six minutes.

There were two maternal deaths. The first was a 44-year-old para xii, gravida xiii, not prenatal, with a twenty-four weeks' gestation, and a blood pressure of 270/165. The patient came to the ward with an examining room diagnosis of uremia. Her symptoms were dizziness, blurred vision, nausea, edema, and four plus albumin was found in the urine. Fetal heart tones were present, and the uterus was one finger above the umbilicus. The urinary output on the first hospital day was 400 c.c., and by her fifth hospital day she had developed a complete anuria. A 6 cm. intraovular bag was placed. During the three-hour labor, which began promptly, the fetal heart tones were lost, and a stillborn infant, weighing one pound, was delivered spontaneously. The patient expired on her seventh hospital day. A post mortem was denied. The cause of death was considered uremia.

The second maternal death was a patient 43 years of age, para xviii, gravida xix, of about thirty-two weeks' gestation, with the membranes ruptured and a blood pressure of 170/110. She had edema and four plus albumin. Medical induction failed. This patient had previously been in the hospital for one week for painless bleeding, but on examination no placental tissue had been palpated, and, after five days of bed rest, she signed her release and went home. At that time, she had a blood pressure of 140/90. When she returned one week later, the edge of the placenta could be felt through a 3 cm. dilated cervix, and a 10 cm. intraovular bag was introduced at 6:30 P.M. on the day of admission. The blood pressure at that time was 180/112, and fetal sounds were present. At 9:30 P.M. (three hours later) the patient became cyanotic and dyspneic, and it was thought that she might be bleeding behind the bag. The bag was removed, and the bleeding found to be minimal, so a second bag was placed. The patient then had a chill, and her blood pressure dropped to 110/60, and her temperature rose to 103° F. Plasma was given and stimulants and oxygen, but in spite of these efforts, the patient continued a downhill course, and expired at 10:30 A.M., sixteen hours after the introduction of the bag, and thirteen hours after the onset of shock. Fetal heart tones were present, and a postmortem section was done, but the baby could not be resuscitated. There was a low-lying placenta, but no retroplacental blood clot and no evidence of bleeding. A post mortem was denied and the cause of death remains undetermined.

Neither of these two maternal deaths can be charged to the method of delivery. Although post mortems were denied, one was without a doubt uremia, and the other was apparently due to some sort of cardiovascular shock, or possibly to a nonconvulsive eclampsia.

TABLE X. PRENATAL CARE OF BLEEDERS

NUMBER OF VISITS	COOK COUNTY HOSPITAL	CHICAGO BOARD OF HEALTH	CHICAGO MATER-NITY CENTER	OTHERS	PRIVATE M.D.	NO RECORD	NO PRE-NATAL CARE
0						1	42
1	5	2	1	1 (Chicago Lying-in)	2		
2	3	5	2		1		
3	3	1					
4	1	1					
5	1	1					
6	1						
7		1					
8	1	2		1 (Infant Welfare)			
9	1						
10	1	1					
Total	17	14	3	2	3	1	42
						Grand Total	82

TABLE XI. PARITY OF BLEEDERS

PARA	PLACENTA PREVIA	ABRUPTIO PLACENTA
0	6	5
i	3	2
ii	19	2
iii	11	2
iv	4	3
v	3	2
vi	4	0
vii	3	0
viii	1	1
ix	1	1
x	3	1
xi	1	1
xii	1	0
Total	62	20

TABLE XII. PERIOD OF GESTATION IN BLEEDERS

WEEKS	ABRUPTIO PLACENTA	PLACENTA PREVIA
24-27	3	11
28-31	5	15
32-35	9	24
36-40	3	12
Total	20	62

TABLE XIII

TYPES OF PLACENTA PREVIA	TYPES OF ABRUPTIO PLACENTA
Marginalis and lateralis	Partial separation
Partialis	Complete separation
Totalis	
Total	Total
38	9
22	11
2	
62	20

TABLE XIV. PRESENTATIONS

PLACENTA PREVIA	ABRUPTIO PLACENTA
Cephalic	Cephalic
Breech	Breech
Transverse (2 with prolapsed cord and hand)	
Double footling	
Single footling	
Total	Total
44	19
11	1
4	
2	
1	
62	20



## Neonatal Deaths

Three infants in this group were less than twenty-six weeks' gestation, and died in the first forty-eight hours after birth, weighing 1 lb., 1 oz.; 1 lb., 3 oz.; and 2 lb., respectively. In each instance there was a severe maternal toxemia.

CASE 5.—L. H., aged 39 years, thirty-six weeks' gestation, para iii, gravida vi, with a blood pressure of 180/110, edema, and four plus albumin. No prenatal care. Fetal heart tones were good. Medical induction failed. On the third hospital day, a 5 cm. extraovular bag was inserted, which was expelled in four hours and fifty minutes. The pains stopped one hour after the bag was expelled, and for twenty-four hours there were no pains. A hot enema and quinine were then given, and labor promptly began, and terminated in a spontaneous delivery two and one-half hours later. The fetal heart tones were good the entire time. The membranes ruptured spontaneously just before delivery. A 6 lb., 5 oz. infant was delivered spontaneously. It had a heart beat, but breathing was not established.

This management is criticized for the delay between the expulsion of the bag and delivery. An attempt should have been made to stimulate the pains earlier. The patient was febrile for three days, and was discharged on her tenth postpartum day.

Of the nine para 0's mentioned in Table III, three have been reported with the eclampsias, two of whom had absent fetal heart sounds, and one was an ill-advised bag. Two para 0's were reported with the intrapartum infant deaths. One of these was the patient with hemoplegia and hematuria and oliguria, who had a 2-pound stillborn infant, and one had the membranes ruptured fifty-six hours on admission, and had a temperature of 101° F. One of the remaining four patients was only twenty-six weeks' gestation, and the other three patients had absent fetal sounds on admission to the hospital.

There were seven patients with intrapartum sepsis, as shown on Table IX. Five went home within ten days, one in fifteen days, and one with manual removal of the placenta was in the hospital thirty-five days. There were sixteen other postpartum morbidities, including the two maternal deaths. All of the remaining fourteen went home in twelve days or less.

TABLE IX. MATERNAL MORBIDITY IN SIXTY-FOUR TOXEMIAS

	HOME
7— <i>Intrapartum</i>	8 days
4 were reported with the eclampsias	8 days
	9 days
	10 days
1 had membranes ruptured for 56 hours on admission	15 days
1 had upper respiratory	10 days
1 retained placenta with manual removal	35 days
16— <i>Postpartum Morbidities</i> —including the two maternal deaths	
All of the remaining 14 went home in 12 days or less	
—	
23 Total patients	

## Bleeders

There were sixty-two placenta previas and twenty abruptio placentas in whom bags were used. Like the toxemias, this group (Table X) had inadequate prenatal care. Forty-two had had no prenatal care, and twenty-five others had attended clinic three times or less.

The parity (Table XI) was from para 0 to para xii, with the largest number of previas falling in the para ii and para iii groups. The largest number of patients with abruptio placenta was found in the para 0 group.

sounds were present, and the position was transverse. Twelve hours later the cervix was completely dilated, but fetal heart tones could no longer be heard. Forty-eight hours after the bag was first introduced and twelve hours after it was removed, a female stillborn infant, weighing 5 lb., 15 oz., was extracted by the breech. The patient ran a fever for three days, but went home on her eighth postpartum day.

CASE 2.—Aged 33 years, para vi, gravida viii, was admitted to Cook County Hospital with ruptured membranes and a prolapsed cord. The cord was replaced, and a 10 em. bag introduced. This failed to produce labor after forty-seven hours, and because fetal sounds were still present, a Porro section was done, but a 7-pound stillborn infant was delivered. The patient ran a septic course for three days, but was able to go home on her fifteenth postpartum day.

Fetal heart tones were absent on admission (Table XVI) in sixteen (25.8 per cent) patients with placenta previa, and in fifteen patients (75 per cent) with abruptio placenta. There were nine intrapartum deaths, ten neonatal deaths, with a total salvage of thirty-five infants. There were three sets of twins, and consequently eighty-five infants are reported.

TABLE XVI. FETAL OUTCOME IN EIGHTY-TWO MATERNAL BLEEDERS

	PLACENTA PREVIA	ABRUPTIO PLACENTA
Fetal heart tones absent on admission	16	15
Intrapartum deaths	8	1 (Twin, 1 lb., 3 oz.)
Neonatal deaths	9	1 (Twin, 1 lb., 2 oz.)
Live births	31	4
Total	64 (2 sets of twins)	21 (1 set of twins)

Of the eight intrapartum (Table XVII) fetal deaths, two have been reported with the failed bags. One set of twins and three single infants weighed 2 pounds or less. There is also an eight months' gestation in this group that had ruptured membranes for one week before admission, and had a temperature of 101° F. The infant's heart tones were lost one hour and twenty minutes after the bag was introduced, and a 4 lb., 4 oz. stillborn infant was delivered.

TABLE XVII. PLACENTA PREVIA FETAL MORTALITY; EIGHT INTRAPARTUM DEATHS

2	were reported with failed bags.
2	Seven month twins. Membranes ruptured forty-eight hours on entrance. First baby breech. Fetal heart tones lost one hour after bag. Weight, 1 lb., 6 oz. and 1 lb., 3 oz. Total labor five hours.
1	Seven months' gestation. Cord and arm prolapsed on entrance. Weight, 2 lb.
1	Six and one-half months' gestation. Membranes ruptured sixty hours on entrance. Weight, 1 lb., 10 oz.
1	Six and one-half months' gestation. Weight, 1 lb., 7 oz.
1	Eight months' gestation. Membranes ruptured one week before admission. Temp. 101° F. Fetal heart tones disappeared one hour and twenty minutes after bag was introduced. Weight, 4 lb., 4 oz.

TABLE XVIII. NINE NEONATAL DEATHS IN PLACENTA PREVIA

1.	6 months	Weight, 1 lb. Lived 1 hour.
2.	6 months	Weight, 1 lb., 4 oz. Lived 36 hours.
3.	6½ months	Weight, 1 lb., 2 oz. Lived 12 hours.
4.	6½ months	Patient bled three weeks at home—shock. Weight, 1 lb., 3 oz. Lived 3 days.
5.	7 months	Weight, 1 lb., 12 oz. Spontaneous breech. Lived 2 hours.
6.	7 months	Weight, 1 lb., 15 oz. Spontaneous. Lived 24 hours.
7.	7 months	4 lb. Transverse. Version and Extraction. Lived 40 min.
8.	7½ months	Weight, 3 lb., 12 oz. Breech extraction—foot and cord prolapsed when bag was expelled. Lived three days.
9.	7½ months	Weight, 2 lb., 3 oz. Spontaneous. Lived 36 hours.

The period of gestation varied from twenty-four weeks to term. Both placenta previa and abruptio placenta occurred most frequently in the group from 32-35 weeks' gestation, and the next most frequent occurrence was in the 28-31 week group.

There were thirty-eight marginal and lateral (Table XIII) placenta previas; twenty-two patients in whom placental tissue partially covered the external os and two in which the external os was completely covered. In each of the total previas fetal sounds were absent, and both patients were multiparas. At delivery, eleven of the abruptio placentas (Table XIII) were completely separated, and nine were partially separated.

As might be expected, eleven of the placenta previa infants presented by the breech (Table XIV), four were transverse presentations, two double footlings, and one single footling. There was one instance of breech presentation among the abruptio placentas.

Ten of the abruptio placentas (50 per cent) and eleven of the placenta previas (17.7 per cent) were brought to the hospital in varying degrees of shock. Thirty of the bleeding patients received from one to four transfusions each. Seven of the placenta previas had hypertension, as did eight of the abruptios. Three other abruptios had direct trauma to the abdominal wall, which probably accounted for the retroplacental clot. In the remaining nine, the etiology is not clear.

A number of the bleeding patients were in early labor, and consequently advanced more rapidly after the introduction of the hydrostatic bag than did the toxemia group. In all cases of placenta previa, the bag was placed intraovularly, and the average length of labor was five hours and fifty-five minutes (Table XV), excluding the two failed bags. There were nine extraovular bags in abruptio placentas, with an average labor of seven hours and thirty minutes, and eleven intraovular bags with an average labor of five hours and forty minutes. Here again the figures show that when the intraovular bag is used the onset of labor is more prompt, and the length of labor is shorter than when the bag is extraovular.

TABLE XV. ONSET OF LABOR AFTER BAG WAS PLACED

PLACENTA PREVIA			ABRUPTIO PLACENTA			
ALL INTRAOVULAR BAGS			EXTRAOVULAR		INTRAOVULAR	
PATIENTS	TIME OF LABOR		PATIENTS	TIME	PATIENTS	TIME
34	Within 30 min.		7	within 30 min.	6	within 30 min.
10	Within 1 hr.		1	within 1 hr.	2	within 1 hr.
4	Within 2 hr.		1	within 4 hr.	2	within 2 hr.
2	Within 3 hr.				1	within 4 hr.
4	Within 4 hr.					
1	Within 6 hr.					
2	Within 7 hr.					
1	Within 9 hr.					
1	Within 11 hr.					
1	Within 18 hr.					
2	Failed					
			<i>Average Length of Labor</i>			
			Intraovular—Placenta previa		5 hr. 55 min.	
			Intraovular—Abruptio placenta		5 hr. 40 min.	
			Extraovular—Abruptio placenta		7 hr. 30 min.	

There were two failed bags among the placenta previas:

CASE 1.—Aged 33 years, para vi, gravida vii, Mexican. No prenatal care. The patient came to Cook County Hospital one month before term with a history of vaginal bleeding for two hours. Sterile vaginal examination revealed a marginal placenta previa. Her pulse was 110, blood pressure 115/65, and membranes intact. Fetal heart tones were 140. The membranes were ruptured artificially, and an intraovular 11 cm. bag was introduced. Quinine and pituitrin failed to produce labor. After twenty hours, the patient developed a temperature of 102° F., and after thirty-six hours the bag was removed. Fetal

There were four fetal deaths in this group (Table XXI)—on antepartum, two intrapartum, and one neonatal. All of the three stillbirths had prolapsed cords on admission. In the neonatal death, the patient entered the hospital with an arm prolapsed to the elbow. This was a seven months' gestation, and was delivered by version and extraction 10 hours, and 50 minutes after the bag was introduced. The infant weighed 3 pounds, 4 ounces and expired fifty-six hours after birth.

The morbidity for the miscellaneous group was eight cases. Two of these morbidities were intrapartum and six postpartum. The average hospital stay was nine and one-half days.

### Summary

One hundred and sixty-four patients are reported in whom a hydrostatic bag was used. There were four sets of twins and hence one hundred and sixty-eight babies. The gross infant mortality was eighty-five. In fifty-one patients fetal heart tones were absent when the patients were admitted to the hospital. There were thirty-four stillbirths and neonatal deaths, of which sixteen were twenty-six weeks or less in gestation, and the infants two pounds or less in weight. The corrected infant mortality is eighteen or ten and seven-tenths per cent (Table XXII).

TABLE XXII. SUMMARY

164 patients in whom a hydrostatic bag was used.
168 infants (four sets of twins)
85 gross infant mortality
51 babies were dead on admission
34 stillbirths and neonatal deaths
16 were twenty-six weeks' or less gestation and two pounds or under in weight
18 corrected infant mortality, or 10.7 per cent

In the group of patients reported here, a large percentage of patients were not good risks for abdominal delivery for one reason or another. It is considered good obstetric practice to deliver patients from below in all instances where the infant viability is questionable. A mother should not be subjected to the risk of major abdominal surgery in the interest of a baby whose chances of survival are already minimal. This error was made in the case of the Porro section following a failed bag, and a stillbirth resulted.

In the seven-year period which this investigation covers, approximately 28,000 babies were delivered at the Cook County Hospital. Only one hundred and sixty-four bags were used, which is a very small percentage of the total. In some of the cases reported the choice of the hydrostatic bag was not wise, and in others too small a bag was used. However, a situation poorly selected for a given procedure, or one which is mismanaged, should not condemn the method used.

The method of delivery is influenced by the duration of the pregnancy, the parity of the patient, and the condition of both mother and baby. When one elects to introduce a hydrostatic bag, there is already an obstetric difficulty. The patients on whom bags were used, for the most part, are patients who were in no condition for abdominal surgery, or in whom the baby was dead or previable. It is not, therefore, reasonable to compare the results of bags with the results of cesarean section.

There were nine neonatal deaths in the placenta previas, of which six were less than two pounds in weight, and the period of gestation in four of these was twenty-six weeks or less (Table XVIII).

There were twenty patients with morbidity, of which nine were intrapartum and eleven postpartum fevers. None of these were seriously ill, and the average hospital stay for the septic group was eleven days, while the average for the afebrile group was nine days (Table XIX).

TABLE XIX. MATERNAL MORBIDITY IN EIGHTY-TWO BLEEDERS

<i>Intrapartum</i> —9 patients
2 Failed bags
2 With nonsterile gauze pack in vagina on entrance
2 Upper respiratory infections
1 Pyelitis
2 Membranes ruptured on admission for more than thirty hours
<i>Postpartum</i> —11 patients
Total—20 patients
Average length hospital stay in the morbidities was 11 days.
Average for the afebrile patients in this group was 9 days.

### Miscellaneous

There were eighteen bags placed for a variety of reasons, and they have been grouped under the heading miscellaneous. Nine of these (Table XX) were used in transverse presentations, two in deflexion attitudes, one with a compound presentation, one double footling with a prolapsed cord, one a single breech with a forelying cord, two cephalics with forelying cords, one ruptured membranes for four days on admission, and one para vi at eight months with a diaphragmatic hernia. This latter patient was dyspneic and had become emaciated from inability to retain food because of mechanical pressure.

TABLE XX. EIGHTEEN MISCELLANEOUS PATIENTS

9 Transverse presentations	2 with arm and cord prolapsed
	2 with arm prolapsed
	1 with membranes ruptured and no pains
2 Face presentations	
1 Compound presentation—head and hand	
1 Double footling with cord prolapsed	
1 Single breech with forelying cord	
2 Cephalics—1 with occult cord; 1 with prolapsed cord	
1 Ruptured membranes 4 days with no pain	
1 Diaphragmatic hernia	
18 Total	

TABLE XXI. FETAL MORTALITY IN MISCELLANEOUS

1 Fetal heart tones absent on admission. Double footling with cord prolapsed.
2 Intrapartum deaths.
Para iii, gravida iv, with arm and cord prolapsed
Para iv, gravida v, with arm and cord prolapsed
Both delivered via version and extraction
Both were eight months' pregnant
1 Arm prolapsed to elbow. In labor on admission.
Delivered by version and extraction ten hours and fifty minutes after bag inserted
Gestation of seven months. Weight, 3 lb., 4 oz.
Expired 56 hours after birth
4 Total

Our indications were as follows:

Placenta previa	15
Abruptio placenta	1
Toxemia	3
Prolapsed cord	2
Pyelitis	1
Failure of medical induction after premature rupture of membranes—7 days	1
Fetal salvage	11
Neonatal deaths	5
Intrapartum deaths	5
Antepartum deaths	2
<i>Period of Gestation</i>	
26-40 weeks	12
31-35 weeks	4
26-30 weeks	4
21-25 weeks	1
Under 20 weeks	2
Multiparas	14
Primiparas	9

DR. G. C. RICHARDSON.—Dr. Webster, in her opening statement, differed with the widespread and extreme condemnation of the bag as presented in the recent literature. Too frequently when one starts out to study a series of cases in this manner, they are apt to be prejudiced in that study. This has seemed quite the opposite in Dr. Webster's case, for she has taken the case histories of the Cook County service and has taken the cases that were operated upon or delivered by those with whom she is associated and in a number of instances has even criticized the choice of the use of the bag.

In preparing to discuss this paper, with the extreme trend of the literature, I felt it might be in keeping with the nature of the paper to review the textbooks on obstetrics and to get an expression as put forth by them. I went over the outstanding textbooks on obstetrics and reviewed their indications for the use of the bag. All expressed the opinion that there was a place for the bag. In one text only was there an expression or intimation that the bag should be completely discontinued in obstetric practice. In studying the opinions set forth in these various textbooks, the indications for the use of the bag numbered some twenty odd, all of which could be included under Dr. Webster's brief classification of the three indications. As to the actual use of the bag there are certain conditions that must be met. There must be some dilatation of the cervix for its introduction or a means of dilating the cervix with the least injury to the tissues involved. Some of the conditions expressed were that you must have a living baby. To that I take exception.

Dr. Webster has by the nature of this study not been able to cover every phase of the use of the bag in obstetrics. It is not possible in such a discussion, to completely cover all the uses of the bag. In the use of the bag in placenta previa and eclampsia we have a wide variation of conditions that must be met: the location of the placenta in placenta previa, the degree of hemorrhage, whether or not we have an outlook for securing a living baby, and last but not least, the time factor. One of the great things that we must consider in the use of the bag is whether the woman can be delivered in appropriate time by the introduction of the bag either to secure dilatation or to induce labor or to facilitate labor that is already in progress. In eclampsia the time element enters again. If we start with the bag and the condition becomes more serious, then having started we are not able to change our course and thus are not able to employ a means that would give a satisfactory result. In saying this I am not criticizing the use of the bag in eclampsia but there are certain cases of eclampsia or uremia where the bag will fail as a result of the edematous type of cervix. In others there is a place for the bag provided the patient is not in condition where the time element requires more rapid delivery than we can expect by the introduction of the bag. In those cases we have to be very careful in the selection of the case. There are various other conditions. We must not have cephalopelvic disproportion whereby after securing adequate dilatation and stimulating labor by the use of the bag, we are still unable to deliver the baby through the pelvis. Some of the errors in the use of the bag are less serious today than they were

It would seem that the hydrostatic bag still has a limited place in the obstetric armamentarium, but no fixed policies can ever apply to its use. Careful consideration of each situation and good obstetric judgment are essential if the best interests of both mother and child are to be served.

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### Discussion

DR. ROBERT M. GRIER.—At the January meeting of this Society, Dr. M. E. Davis reported the results of the treatment of placenta previa at the Chicago Lying-in Hospital. In this report he more or less condemned the use of the hydrostatic bag for this condition. His arguments were quite convincing. I must admit that my experiences with it have given me many headaches. It does not work as well as Nature, but neither does any man-made effort. It is an artificial attempt to handle an abnormality, and does have a definite place in our armamentarium.

When one studies the situations described in this series of cases at the Cook County Hospital in seven years, it is obvious that they have had to deal with more extreme problems than most of us will see in private practice in a lifetime. I do not think the Lying-in Hospital has the ignorance and shiftlessness to deal with in their patients which is true of the Cook County Hospital.

Some of the women with toxemia who were delivered after induction of labor with a bag might well have been delivered better by cesarean section. It seems to me that if the toxemia is severe enough to warrant prompt delivery, a cesarean section done under local anesthesia is a quicker and more certain way of terminating the pregnancy. The time expended in establishing labor in addition to labor itself, may be time enough for eclampsia to develop. When the toxemia is progressing in this direction in spite of conservative management, the only thing we can do for these women is to deliver them as soon as possible. I have very little confidence in our ability to abort eclampsia in any other way. It appears much better to get rid of the cause which apparently is an incompatibility between mother and fetus.

This does not mean that either cesarean section or the hydrostatic bag should be used when a woman is in the eclamptic state. The pregnancy here must be disregarded while an attempt is made to temporarily reduce the toxemia. It is difficult to decide when this has been accomplished. If it has, then it is only temporary, and a cesarean section under local anesthesia is the more efficient method of delivery.

The author has stated that another indication for the bag is placenta previa and abruptio placenta. In the latter condition I think cesarean section is safer because we are dealing with concealed hemorrhage. No time should be wasted with bag induction. In the former it is often too late to attempt cesarean section and the Voorhees bag has a definite place. It can usually be employed to control hemorrhage quicker than an operating room can be prepared and this is life saving time. It will be more often successful in getting a live baby than will Braxton-Hicks version. In this procedure one elects to use the baby as a tampon regardless of the danger to the child. Away from hospital facilities it may be a life saving procedure. If the viability of the baby is questionable anyway, it is justified.

When one is dealing with placenta previa and a baby that is near term, and there is time to prepare for the cesarean operation, and we are sure of our diagnosis, be it only a low-lying placenta, I think this is the safest procedure for both mother and baby. Especially is this true when the cervix is uneffaced and undilated, be it in a primipara or multipara. I believe it is better to do too many cesarean sections under these circumstances than too few.

At the Evanston Hospital in over 10,000 deliveries we have inserted the Voorhees bag only 23 times. One mother was lost in this procedure. This was a case of gross neglect on the part of an inexperienced man who failed to have consultation until it was too late.

## AN ANALYTICAL SURVEY OF ECLAMPSIA

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THIS survey is concerned with a careful attempt to analyze a group of pregnancies complicated by eclampsia, consisting of 62 cases which were treated in the Division of Obstetrics from January, 1927, to December, 1945. Although studies and surveys have been reported in the literature from time to time, we feel that additional data and studies of eclampsia will act to emphasize certain factors of diagnostic and prophylactic importance.

In this study, it was attempted to correlate our findings with possible relationships to age, race, parity, signs and symptoms, seasonal variations, and type of delivery.

From Jan. 1, 1927, to Dec. 31, 1945, there were delivered 14,374 ward patients, and in this group there occurred 62 cases of eclampsia, for a percentage of 0.43, or one eclamptic in 231.8 delivered cases.

In the first five years, from 1927 to 1931 inclusive, there were delivered 3,223 cases, and in this group there occurred 20 cases of eclampsia or 0.62 per cent (1 in 161.1 cases). While during the last five years from 1941 to 1945, inclusive, there were delivered 4,233 cases, and in this group there occurred 17 cases of eclampsia, or 0.4 per cent (1 in 248.4 cases). From these figures it will be noted that the frequency of eclampsia is decreasing (Fig. 1).

The age at which eclampsia occurs is of considerable interest to the student of this complication. The youngest patient in our survey was 15 years old, the oldest being 44 years. Hinselmann found that 90 per cent of all patients with eclampsia are between the ages of 14 and 30 years.

Fig. 2 illustrates the occurrence of eclampsia according to age.

It can be observed that 83.8 per cent occurred between the ages of 15 and 30 years, 69.3 per cent occurred between the ages of 15 and 25 years, and 46.7 per cent occurred between the ages of 15 and 20 years. From these observations it may be noted that practically half of our cases occurred between the ages of 15 and 20 years.

In this series, eclampsia occurred in primiparas 41 times and in multiparas 21 times, an approximate ratio of primiparas to multiparas of 2 to 1. It was found that 66.1 per cent of the eclamptics were primiparas. Other observers have found a ratio of 6 to 1 when comparing the frequency of eclampsia in primiparas and multiparas. Some others have given figures of approximately 80 per cent of eclampsia occurring in primiparas (Fig. 3).

*Racial Incidence of Eclampsia (White and Negro).*—It was found that 56.4 per cent of the eclamptics were Negroes, and 43.5 per cent were white.

Attempts have been made to determine the part played by seasonal variation in eclampsia, and also the effects of abrupt changes in barometric pressure. We have attempted to note that frequency of eclampsia in the various months, and also during the different seasons. The most cases occurred in June, for a total of almost 16.1 per cent of all cases in our series.

According to seasons, the frequency of occurrence was as follows: summer, 33.8 per cent; autumn, 22.5 per cent; winter, 25.8 per cent; spring, 17.7 per cent.



some years ago inasmuch as we have the sulfonamides to combat infection and penicillin to use for the same purpose.

There are also contraindications. One is the possibility of infection, another is the dislodgment of the presenting part and the possibility of producing a prolapse of the cord. It seems quite obvious that Dr. Webster has given this very serious thought. She has presented cases with a bad outcome and those with good results. It would seem that her case in defense of the bag certainly is worthy in selected cases. The criticism of its use in some of these cases indicates to me that her idea is to be very selective in the cases in which she pursues this course to termination of labor.

DR. W. C. DANFORTH.—I feel, as the essayist said, that in a certain percentage of placenta previas, particularly if the viability of the child is in question and also if we are dealing with a multipara, that the use of the bag still has a definite place. I do not believe we should completely do away with it, though the frequency of its use is definitely less than it was.

DR. EDWARD L. CORNELL.—During the years 1917 to about 1927, when I was associated at the Lying-in Hospital with Dr. DeLee, we used the bag frequently. At that time he wanted some means of determining how much dilatation we had with the use of the bag and set me to work on it. I developed the ring bag, as some of you know. We used the bag at that time in atresia and placenta previas and in multiparas in which we wanted to induce labor, and, in fact, we more or less generally used it. Our results for the period of time of the study were such that Dr. DeLee decided that the bag was being used altogether too much. We developed a technique there which, I think, if we are going to use the bag, perhaps it would be helpful.

If the cervix is long and not dilated in a multipara and you put in a 10 cm. bag, the bag floats up above the cervix because it is impossible for the stem of the bag to fit in. The head is displaced and pushes the bag over to the side so that you have two objects there instead of one attempting to dilate the cervix. The reason we have so many different size bags is for this purpose. One should start with the smallest bag possible, 4 or 5 cm. bag, which is more apt to fit in properly. The head being down, the bag will not displace it to the same degree as the large bag. After the 4 or 5 cm. bag has been expelled, then a larger bag is inserted. This is the technique that should be followed in a primipara. If, on the other hand, the cervix is dilated and more or less fixed, a large size bag can be placed, the stem will be down in the cervix and the head cannot get in between the wall of the uterus and the bag.

If you wish to keep that bag in position, you must put a weight on it. We put on anywhere from a one-half to a two and one-half pound weight attached over a traction pulley to the end of the bed, thus having that weight constant all the time. This is apt to put the patient into labor much sooner.

As I said, we came to the conclusion that the bag was being used altogether too often, so that we used it chiefly after 1927 in eclamptics and in multiparas in whom we wished to induce labor for various reasons. At that time we used to think we should induce labor if the patients went over term for two weeks or more.

Gradually, I have discontinued the use of the bag. I do not use it in placenta previa or in atresia; in fact, I have not used a bag in private practice in the last seven or eight years.

DR. WEBSTER (Closing).—Dr. Richardson's point regarding conditions must be considered in each individual instance. There are certain conditions of the cervix which would not permit the introduction of the bag.

In reply to Dr. Cornell regarding weights; weights are used quite often in toxemias, but we have been a little fearful of the use of weights when there is a low-lying placenta. Dr. Hillis used to insist that the resident stay with the patient who had a low-lying placenta and exert just enough digital pressure on the stem of the bag to control the bleeding. He feared that a weight of one or two pounds would start a tear in the cervix that could not be controlled.

Fig. 4 shows the frequency of eclampsia occurring during the various months and also the mortality incidence. It is not apparent whether the frequency of eclampsia during a certain month of the year bears any relationship to mortality.

It is of interest to note the relative frequency of the various premonitory signs and symptoms of eclampsia. Table I illustrates the frequency of the various signs and symptoms as they occurred in our group of eclamptic patients.

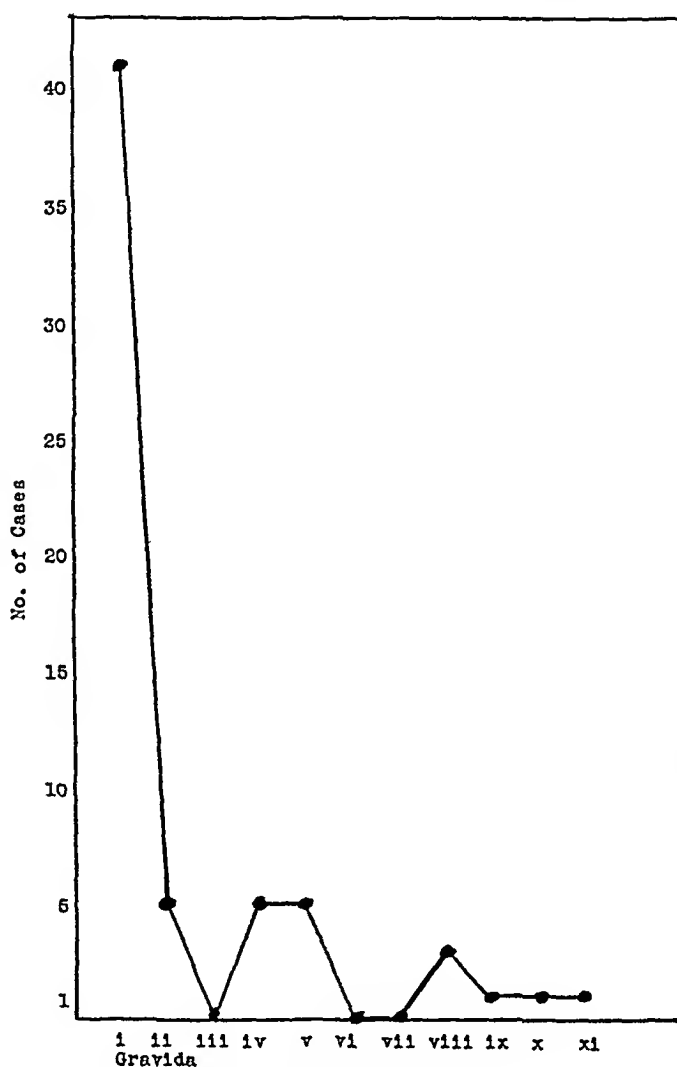


Fig. 3.—The frequency of eclampsia in primiparas and multiparas.

It may be noted that hypertension, edema, edema associated with rapid gain in weight, and albuminuria occurred in 100 per cent of these cases.

In reviewing the blood pressure estimation of our cases, we find that the highest recorded blood pressure was 290 systolic, and the lowest systolic blood pressure recorded in this group of eclamptics was 140. The highest diastolic blood pressure was 200, and the lowest 70. Strange as it may seem, the patient with the systolic blood pressure of 290 and the one with diastolic blood pressure of 200 made a good recovery.

The patients in this summary were classified according to the time that eclamptic seizure occurred, that is, ante partum, intra partum, and post partum. Table II illustrates the number of patients in each group.

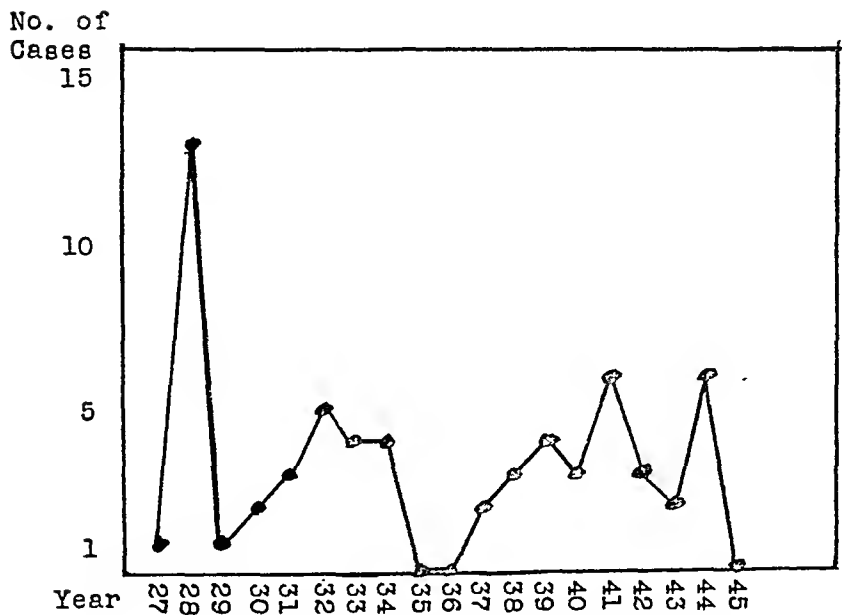


Fig. 1.—Number of cases of eclampsia occurring from Jan. 1, 1927, to Dec. 31, 1945, by years.

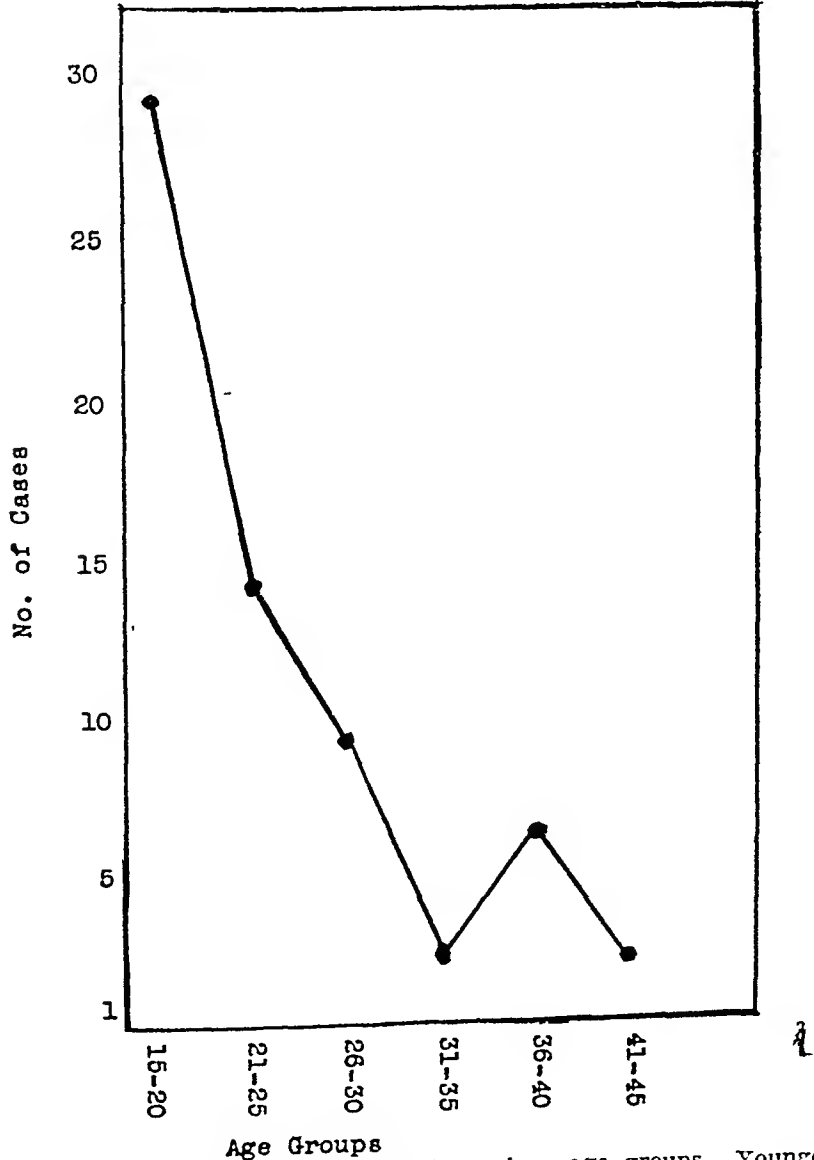


Fig. 2.—Number of cases of eclampsia occurring in various age groups. Youngest patient—15 years. Oldest patient—44 years.

TABLE II

Ante partum	45	72.5 per cent
Intra partum	11	17.7 per cent
Post partum	6	9.6 per cent

TABLE III

Patients	62	(Eclampsics)
Patients undelivered	7	(Six died undelivered, and one signed release after recovery and was delivered elsewhere)
Patients delivered	55	(Three sets of twins)
Babies born		
Alive	41	
Stillborn	17	
Total	58	(Including three sets of twins)

TABLE IV. BABIES DIED FOLLOWING DELIVERY

1. Spontaneous delivery, died in eleven hours, vertex, premature (seven months), showed evidence of birth injury, tentorial tear and 4 plus Wassermann (mother)
2. Low forceps died in fifteen hours, vertex, full term (one of twins)
3. Cesarean section, died third day, eight and one-half months, toxemia
4. Forceps, died sixth day, full term, toxemia

The fetal mortality was 37.7 per cent. If we include the four infants who died following delivery, then the total fetal mortality is 27 babies, or 44.2 per cent.

TABLE V. STILLBORN

1. Vertex, spontaneous, macerated, seven and one-half months
2. Breech, second of twins, stillborn, term
3. Vertex, one of twins, spontaneous, cerebral hemorrhage, term
4. Vertex, spontaneous, hemorrhage into parenchymous organs, ateleetasis
5. Vertex, version, internal podalic version, subdural hemorrhage, term
6. Vertex, low foreeps, hemorrhage into parenchymous organs, term
7. Vertex, spontaneous, macerated, term
8. Vertex, spontaneous, macerated, seven and one-half months
9. Vertex, low forceps, stillborn term
10. Hysterotomy, eight and one-half months, sterilization
11. Vertex, spontaneous, seven months
12. Vertex, spontaneous, seven and one-half months
13. Breech, spontaneous, macerated, seven and one-half months
14. Breech, spontaneous, seven months
15. Vertex, spontaneous, term
16. Vertex, spontaneous, term
17. Vertex, spontaneous, macerated, seven months

TABLE VI. TYPE OF DELIVERY

Spontaneous	33
Foreeps	15
Breech	4
Cesarean section	4
Internal podalic version	2
	58 deliveries
(All four cesarean sections were performed on patients after recovery from eclampsia)	
(Six undelivered infants, 58 plus 6 = 64 infants for 61 patients.	
One patient signed release after recovering from eclampsia and delivered elsewhere)	

TABLE I. SYMPTOMS AND SIGNS

Hypertension	62
Edema and rapid weight gain	62
Edema	35
Rapid weight gain	27
Albuminuria	62
Eye symptoms	25
Nervous manifestations	10
Headache	43
Dizziness	14
Insomnia	4
Gastrointestinal	
Nausea	8
Heartburn	9
Vomiting	14
Pain	
Substernal	19
Epigastric	8
Dyspnea	8
Palpitation	7
Dysuria	3
Hematuria	1

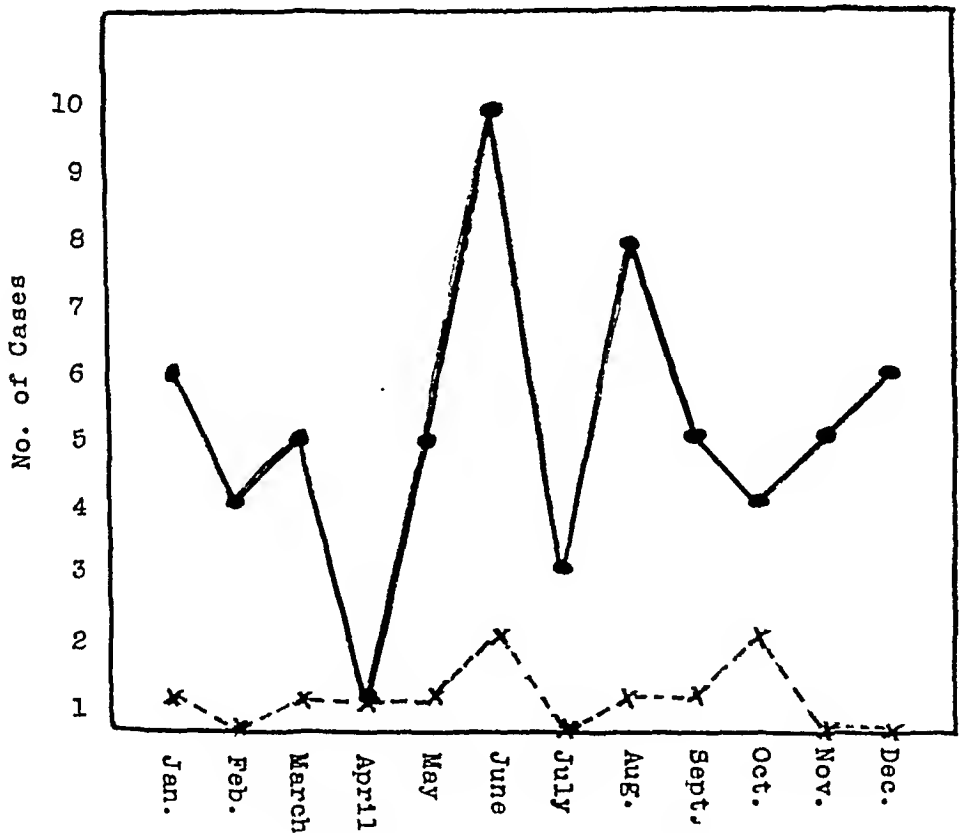


Fig. 4.—The frequency of eclampsia during the various months and the mortality during these months.

Arnell in his series found the following: ante partum, 52.1 per cent; intra partum, 21.1 per cent; post partum, 26.8 per cent.

Of the 62 eclamptic patients, 55 of them were delivered of 58 babies, there being three sets of twins. Six patients died undelivered, and one patient signed a release and was delivered elsewhere.

It is to be noted that four babies were born alive and died following delivery. The periods of survival ranged from eleven hours to six days (Table IV).

The patients in this survey were delivered as shown in Table VI.

From Table VIII it may be observed that maternal mortality in this series was 16.1 per cent. Five cases, or 50 per cent of our fatalities from eclampsia occurred during the year 1928. Since 1942 there has not occurred a fatality from eclampsia, and, what is more, in 1945 there did not occur a single case of eclampsia, although the reduction does not hold for the total number of toxemias.

TABLE VIII. YEARS OF OCCURRENCE OF MATERNAL MORTALITY

1928	5 deaths
1932	1 death
1938	1 death
1939	1 death
1941	1 death
1942	1 death
	<hr/> 10
No deaths since 1942	

The factor responsible for the decrease in the incidence of eclampsia is the early detection of and institution immediately of proper treatment for pre-eclampsia, and the education of the public to the importance of prenatal care.

It may be observed that all the fatal cases were without adequate prenatal care. With the advent of improved prenatal care it can be observed how important prenatal care is to the pregnant woman.

In this series of 62 eclamptic patients, 48 patients had inadequate prenatal care and 14 patients were classed as having no prenatal care at all. From these figures one need not ponder very much as to the important factor in preventing this dangerous and often fatal complication in the pregnant and delivered patient.

TABLE IX. PRENATAL CARE, ITS RELATION TO MORTALITY AND ECLAMPSIA

CARE	NO. CASES	MORTALITY
Inadequate	48	6 or 12.7 per cent (1 in 8)
None	14	4 or 28.5 per cent (1 in 3.5)

It will be noted that the mortality is more than twice as great in the patients who did not receive prenatal care at all as compared with those patients who received inadequate prenatal care. For example, it may be observed in Table IX that the maternal mortality in the eclamptic series was 1 in 8 patients for those who received inadequate prenatal care, and rose to the appalling figure of 1 in 3.5 patients, who received no prenatal care whatsoever.

In this series of 62 cases of eclampsia we have selected two cases of interest.

Case Reports

CASE 1.—A young Negro woman, 16 years old, gravida i, 8 months' gestation, with inadequate prenatal care, was admitted to the hospital with a blood pressure of 160/80, in convulsions. Treatment was instituted. She improved and recovered from the eclamptic attack, remaining in the hospital for ten days. She then signed a release against the advice of the staff. One month later she was again admitted with convulsions, in eclampsia with a blood pressure of 150/100. This time she had approximately 18 convulsions, 11 during the time she was in the delivery room. She was delivered of a living infant, and, eight days later, after recovery, signed a release and left the hospital. Both mother and infant apparently were in good condition.

TABLE VII. ANALYSIS OF ECLAMPTIC PATIENTS WHO DIED

AGE (yr.)	RACE	GRAV- IDA	GESTA- TION (mo.)	PRE- NATAL CARE	NO. CONVUL- SIONS	SIGNS AND SYMPTOMS	TYPE DELIVERY	BABY	REMARKS
38	Negro	xi	6½	None	3	Convulsion, coma. BP 240/148; plus 4 alb.; NPN. 24; CO <sub>2</sub> , 44.8	Not delivered	Not delivered	Coma, died undelivered four and one-half hours after admission
16	Negro	i	7	Insufficient	?	Premature separation placenta. BP 156/110; plus 4 alb. Intrapartum eclampsia, died 9 days later from sepsis	Spontaneous	Stillborn, 4½ lb. macerated	Intrapartum eclampsia
30	Negro	i	9	Insufficient	1	Convulsion, coma. BP 200/150; plus 4 alb.; NPN. 28; uric acid 9.88; CO <sub>2</sub> , 37.2; eye grounds normal	Spontaneous	Stillborn	Sudden death (cardiac) fifth day
17	Negro	i	9	Insufficient		Convulsions. BP 150/100; plus 2 alb.; bl. sug. 82; NPN. 30.6; creatinin 1.4; uric acid 6.9; CO <sub>2</sub> , 56.64	Post mortem	Dead	Died five hours after admission
27	Negro	v	9	Insufficient	3	Convulsions, coma. BP 220/180; plus 3 lb.; NPN. 28; uric acid 5.32; protein 6.36; alb. 3.88; globulin 2.48; bl. sug. 75	Post mortem	Dead	Died fourteen hours after admission
38	White	v	7	Insufficient	3	Convulsions, coma, anuria. BP 150/110; bl. sug. 108; NPN. 55.5; urea 30.61; creatinin 2.22	None	Not delivered	Died six hours after admission
32	Negro	viii	9	Insufficient	5	Second day postpartum convulsion. BP 240/100; bl. sug. 130; NPN. 30.44.	Spontaneous	Living	Died ten hours after admission
22	White	i	9	None	8	Convulsions. BP 226/140; plus 3 alb.; hyaline and gran. casts; bl. sug. 122; NPN. 37.72; creatinin 1.72; uric acid 5.5	Induction of labor internal podalic version and traction	Stillborn	
39	White	i	7	None	Many	Convulsions. BP 245/74	Postmortem cesarean section	Dead	Died a few minutes after admission
28	White	i	7	None	Many	Convulsions, coma. BP 184/124; plus 4 alb.; hyaline and gran. casts; bl. sug. 75; NPN. 34.08; blood urea 16.51; creatinin 1.43; uric acid 5.7; CO <sub>2</sub> , 45.05; eye grounds hemorrhagic retinitis	Not delivered	Not delivered	Died twenty hours after admission, pulmonary edema

## SCOPOLAMINE AND APOMORPHINE IN LABOR

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Medical School)

DURING the past fifteen years the Boston Lying-in Hospital has taken an active part in developing a routine of pain relief in labor that would secure a high degree of amnesia with safety to the mother and with minimal effect upon the child. A constant guiding principle observed in the practice of employing pharmacologic agents for the purposes of accomplishing obstetric amnesia and analgesia has been little or no interference with the natural forces of labor. We maintain that a well-conducted spontaneous labor with intelligent supervision of the physiologic activity and needs of mother and child still remains the ideal method of delivery. We also should like to emphasize that the knowledge, experience, skill, and attention of the members of the obstetric team, rather than the drug-combination or technique of administration are the real determinants of the degree of safe relief to the parturient and her child.

Over a period of years we have found the most constantly useful drug in producing amnesia to be scopolamine. Our most successful methods of obstetric amnesia and analgesia include its use.

Clinically,<sup>1-7, 10</sup> it has been shown repeatedly that there are no demonstrable changes in vital fetal functions when scopolamine is administered to the mother. Experimentally,<sup>8</sup> Snyder has observed that fetal activity persists, even though scopolamine in large doses are injected directly into the umbilical vein.

Clinically, a major undesirable effect of scopolamine is the relatively frequent occurrence of excitement states. In the practice of anesthesiology and allied fields of medicine,<sup>9</sup> apomorphine has been employed as a physiologic antagonist to states of delirium induced incidental to the use of various depressant drugs. In a review of the available medical literature, we note that the first attempt to use the combination of scopolamine and apomorphine in obstetrics was that by H. H. Johnson<sup>3</sup> in 1925. For the past few years we<sup>10</sup> have employed apomorphine in subemetic doses to effect sedation of the excited patient encountered in our administration of pain-relieving drugs at the Boston Lying-in Hospital. This interest led us to a more systematic clinical study of this drug-combination which serves as the basis for this report.

### Procedure

We have employed the product marketed as scopolamine hydrobromide in fresh soluble tablet form. Irving<sup>10</sup> has found no essential difference in the production of excitement between the levo-rotatory and dextro-rotatory forms, nor between the ampules and the tablets of scopolamine.

Scopolamine is the most reliable amnesic drug available. It produces psychic sedation and dreamless sleep. Among its parasympatholytic effects are dilatation of the pupil, dryness of mucous membranes of the respiratory tract, acceleration of pulse, prevention of the vagal type of carotid sinus syn-



CASE 2.—This patient had eclampsia with her first pregnancy, and was delivered of a stillborn child five years before this pregnancy.

She was a white, 23-year-old pregnant woman, with inadequate prenatal care, admitted to the hospital in active labor. Convulsions occurred during labor, with blood pressure of 166/84. This patient was delivered of a living infant weighing 9 pounds, 10 ounces, and mother and child left the hospital in good condition.

### Summary

1. This survey included a series of 62 cases of eclampsia which occurred from January, 1927, to December, 1945. During that period, 14,374 cases were delivered, the percentage of eclamptic patients being 0.43 per cent, or 1 eclamptic in 231.8 delivered patients.

2. There occurred in the first five years, 1927 to 1931 inclusive, 20 cases of eclampsia in 3,223 delivered patients for a percentage of 0.62, while the number of eclamptics for the last five years, 1941 to 1945, inclusive were 17 in 4,223 delivered patients, for a percentage of 0.40. In the first five years the frequency was one eclamptic in 161.1 delivered cases, while in the last five years there occurred 1 eclamptic case in 248.4 delivered cases, showing a decrease.

3. Practically half of our cases of eclampsia occurred between the ages of 15 and 20 years (46.7 per cent).

4. The occurrence of eclampsia in primiparas and multiparas was approximately 2 to 1.

5. The frequency with which eclampsia occurred during the various seasons are as follows: summer, 33.8 per cent; winter 25.8 per cent; autumn, 22.5 per cent; spring, 17.7 per cent.

6. All of our patients showed the following: hypertension, edema, and albuminuria.

7. Eclampsia occurred as follows: ante partum, 72.5 per cent; intra partum, 17.7 per cent; post partum, 9.6 per cent.

8. The fetal mortality was 37.7 per cent. If we included four infants who died between eleven hours and six days following delivery, the fetal mortality would rise to 44.2 per cent.

9. In this series of 62 cases of eclampsia there were 10 maternal deaths for a maternal mortality of 16.1 per cent.

It should be noted that the mortality was over two and one-fourth times as great in the patients who have had no prenatal care as compared with those who had inadequate prenatal care.

### Conclusions

This study merely substantiates the conclusions arrived at from other similar studies that prophylaxis, education and adequate prenatal care is the answer to the control and prevention of eclampsia.

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perience of the house officer are more often reflected in his judgment of preanesthetic medication than in any other phase of his development. Experience in the use of this routine of administration, particularly with regard to adjustment of dose, route, and time factors in relation to reflex irritability result in increasing success.

The actual administration of drugs are carried out by our nursing staff.

To obviate too great a discrepancy in the administration of the drugs employed, the following routine was finally adopted.

*Preanesthetic Medication for Patients in Labor*

I. For psychic sedation:

Seconal gr. iii, by mouth or rectum (following admission enema)

II. For purposes of amnesia and analgesia:

A. Initial medication:

Scopolamine

Apomorphine gr.  $\frac{1}{400}$

Administer when patient is making progress and begins to mind her pains.

B. Second medication:

Scopolamine gr.  $\frac{1}{150}$

Apomorphine gr.  $\frac{1}{50}$

Administer  $\frac{3}{4}$  of an hour after A.

C. Subsequent medication:

Scopolamine gr.  $\frac{1}{150}$

Apomorphine gr.  $\frac{1}{50}$

Administer following B, and every two hours thereafter.

III. Standing Nursing Orders:

A. Except for secenal, all routine medication is to be administered intramuscularly.

B. Any change from routine medication must be checked before administration by resident physician.

C. Prior to initial medication, dentures are removed, and canvas bed-sides are placed on beds.

D. Apomorphine in doses of not over  $\frac{1}{50}$  grain may be administered as often as ordered by house officer; minimal intervals of 15 to 30 minutes must be observed.

The house officer is encouraged to order apomorphine if the patient shows cortical excitation.

IV. Contraindications:

A. Do not use routine medication when excitement may be due to oxygen want, e.g., cases presenting shock, respiratory obstruction, or pulmonary edema associated with the pre-eclamptic toxemias.

B. Do not use in Class I or I A Cardiacs.<sup>14</sup>

Secenal was selected as the barbiturate of choice for hypnosis, for it not only is a member of the short-acting barbiturates, but also has never been involved in respiratory accidents or deaths at this hospital.<sup>10</sup> Several modifications of our original regimen of medication were made. Our first efforts involved the use of 0.6 mg. of scopolamine and 1.2 mg. of apomorphine, followed by successive doses of 0.3 mg. of scopolamine and 1.2 mg. of apomorphine every two hours, but vomiting followed frequently. With the use of 0.6 mg. of each of the drugs initially followed in an hour and repeated two hourly thereafter with 0.3 mg. of scopolamine and 1.2 mg. of apomorphine, emesis was reduced, but amnesia-

drome (i.e., bradycardia, lowered arterial tension, and decreased pulse pressure), relief of bronchospasm, and, in certain instances, laryngospasm. Among its undesirable effects are flushing and dryness of the skin, particularly a flushed face, circumoral pallor, augmentation of sympathomimetic visceral traction reflexes especially in patients representing autonomic imbalance, and a cortical effect of uncontrollable excitement. Other very occasional untoward effects observed by us have been edema of one or both eyelids, edema of one or both lips and edema of the uvula. Although scopolamine may increase the maternal respiratory rate, we have observed no comparably demonstrable effect on fetal respiration.

Scopolamine may be administered by any route. Maximum effects may be expected within thirty minutes following subcutaneous or intramuscular injection. These effects occur in about one-fourth of the time when administered by the intravenous route. The duration of its effect is about two hours.

Apomorphine HCl is comparatively unstable in solution. The United States Pharmacopoeia<sup>12</sup> recommends that it be discarded if it imparts an emerald-green color when shaken with 100 parts of distilled water. However, we have found no essential change in the clinicopharmacologic actions of apomorphine solutions. Experimentally, there exists supportive evidence in the work of Garrell and Gray.<sup>13</sup>

To facilitate the use of apomorphine for our nursing staff we prepare solutions of the drug daily under sterile conditions. The solution is prepared by dissolving four tablets of  $\frac{1}{10}$  grain (6 mg.) each, into 20 c.c. of sterile saline solution. This solution is contained in a sterile glass vial of 20 c.c. capacity, provided with a sterile rubber cap. The vial is then labeled "apomorphine solution, 1 c.c. =  $\frac{1}{50}$  grain, 1.2 mg." and is placed in a dark area. Sterile normal saline solution is used as the diluent to prevent possible laking of the red blood cells should the solution be injected intravenously. Apomorphine solutions are rapidly absorbed from any parenteral site. Its maximal effects occur in about twenty to thirty minutes when injected intramuscularly or subcutaneously. If given by the intravenous route, these effects occur in about one-half of the time. The duration of effect lasts about two hours. When employing the intravenous route, the rate of injection of apomorphine solutions should be slower, taking about three to five minutes. The low threshold to nausea and emesis in the obstetric patient is too well known to need further emphasis.

Although apomorphine does not appear to potentiate directly the amnesic effect of scopolamine, it does appear to potentiate its analgesic action. It does this with but little or no apparent effect on the forces of labor and no observable depressant effect on the vital functions of the newborn.

In subemetic doses, apomorphine seems to have a central medullary and supramedullary action antagonizing the untoward scopolamine effects. Increasing the dosage of apomorphine results in stimulation of other medullary functions, more especially the hiccup, salivary, and vomiting centers.

The sedative dose of apomorphine has not been definitely established and varies greatly, depending on the existent state of cortical irritability. In adequate subemetic dosage the delirium induced by scopolamine is completely controlled. The patient becomes quiescent, but neither central depression nor change in vital functions of mother or fetus are usually manifest. Clinically, we were unable to observe any noticeable peripheral action of apomorphine.

### Administration

The results of any method to effect obstetric analgesia and amnesia are no better than the knowledge, training, experience, and skill of the personnel employing that method. At the Boston Lying-in Hospital the house officer on duty orders the medication for the obstetric patient. The training, attention, and ex-

TABLE I. AMNESIA FOR FINAL GROUP OF SERIES

	NO. OF CASES	PER CENT DISTRIBUTION
A. Complete amnesia	175	58
B. Cloudy recall of isolated incident	53	18
C. Cloudy recall of more than one incident	41	14
D. Clear recall of more than one incident	28	9
E. Orderly recall of several incidents	3	1

Considering the last group (E) as failures and excluding the group (D) with clear recall of more than one incident, the effectiveness of this drug-combination reaches 90 per cent. It is interesting to compare the effectiveness of this method of producing amnesia-analgesia with other studies made and reported at this hospital. Table II shows the comparative amnesic effect on the mother.

TABLE II. AMNESIA COMPARED WITH PREVIOUS REPORTS

METHOD (DRUG COMBINATION)	PER CENT EFFECTIVENESS	PERIOD
Morphine-scopolamine	39	Early <sup>1</sup>
Demerol-scopolamine	72	Recent <sup>16</sup>
Barbiturate-scopolamine	86	Mid <sup>1, 10</sup>
Apomorphine-scopolamine	90	Present

Consequently, if we group (A), (B), and (C) in Table I together, we arrive at the figure of 90 per cent satisfactory amnesia. This compares very favorably with any of the previous studies in this hospital. In the groups (D) and (E) composing 10 per cent of unsatisfactory amnesia in this series, the patients received but a single dose of medication and with too little time for this dose to become maximally effective, or the medication was administered too late, or the patient failed to receive her medication at the desirably effective intervals, or the dosage of either premedicant was subminimal.

In the present study no serious untoward maternal or fetal effects were encountered. No cases of pulmonary complications or crises as pulmonary edema were seen. The untoward effects of scopolamine were well controlled when apomorphine was adequately administered.

Table III is an attempt to correlate the number of doses employed and the degree of amnesia-analgesia in the group of cases presented in Table I.

TABLE III. AMNESIA CLASSIFIED BY DOSAGE OF PREMEDICATION

NO. OF DOSES OF SCOPOLAMINE AND APOMORPHINE	GROUP A		GROUP B		GROUP C		GROUP D		GROUP E	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
One	10	18	7	12	20	35	17	30	3	5
Two	73	61	22	18	18	15	7	6	0	0
Three or more	92	74	24	20	3	2	4	3	0	0

We may note that there is greater effectiveness of amnesia with the increase in the number of doses of premedicants. If the patients received three or more doses of scopolamine-apomorphine, the number of cases having complete amnesia was increased to 74 per cent, while those having satisfactory amnesia were increased to 96 per cent. We observed that the minimally effective amnesic state was usually reached about one-half to three-quarters of an hour following the second intramuscular dose of scopolamine-apomorphine.

analgesia was not as complete as we had hoped it would be. We then administered an initial dose of 0.6 mg. of each of the drugs, followed in one hour with 0.45 mg. scopolamine and 1.2 mg. of apomorphine, and two-hourly thereafter by 0.3 mg. of scopolamine and 1.2 mg. of apomorphine, with pronounced improvement in amnesia-analgnesia as well as in reduction of emesis; in fact, no more frequent vomiting than that seen in the unmedicated obstetrical patient.

With the prevalent nursing shortage our next step was further simplification of the regimen of medication. We studied the preparation of sterile solutions of apomorphine in rubber-capped containers, and observed no clinical-pharmacological changes. Interval doses of 0.6 to 1.22 mg. of apomorphine were now used whenever necessary to potentiate the sedative action of scopolamine or treat the symptom of overactivity during contractions in labor. The largest number of such interval doses given to any one patient was five doses of 1.2 mg. of apomorphine during a single one-hour period with desirable response.

It should be emphasized that the effective therapeutic dose of apomorphine varies with the existing state of cerebral irritability. The incidence of "slow" babies during this entire clinical investigation was very low.

### Clinical Studies

Our experience with scopolamine-apomorphine amnesia and analgesia is limited to obstetric patients. The drug was used primarily as a premedicant during the first and second stages of labor to antagonize the marked overactivity encountered when scopolamine is used either with or without barbituric acid derivatives. Finally, we evolved a system of administration of these drugs where amnesia was complete, analgesia satisfactory, excitement markedly decreased and controllable, emesis reduced to a minimum, less strain put on the nursing staff, curiosity and interest of the house-staff is aroused, the labor room is comparatively quiet, and a method with reasonable safety for both mother and her baby.

### Evaluation of Method

To evaluate the effectiveness of these premedicants, each patient was interviewed soon after emergence from anesthesia, the following day, and at various subsequent periods during her hospital stay. When seen soon after emergence the effectiveness of premedication more closely approximated to 100 per cent. However, when interviewed on succeeding days, it was observed that the patient-response to her medication during labor became influenced by uncontrollable factors, e.g., suggestion by her neighbors, visitors, and others. It was also learned that patients could not differentiate between amnesia and analgesia, for this reason the term amnesia-analgnesia is used.

These several findings were well illustrated by a study of multiparas to determine the comparative amnesic-analgnesic effectiveness of this method to their previous experience with pain-relieving drugs during labor. It was revealed that about 11 per cent of this group were indifferent to this form of medication, whereas 47 per cent thought it better than any previous experience, 14 per cent thought this method certainly as good, and about 28 per cent were not certain whether his method was quite as good as some of their previous experiences. All primiparas were pleased with this method of amnesia-analgnesia during labor. By and large the induction and emergence phases were pleasant and peaceful, and devoid of discomfort for the mother.

The optimal routine of medication was finally studied on the last 300 cases of our series. Following this series over 1,000 more patients have received this regimen of medication. The data in the former group may be summarized as to amnesia-analgnesia in Table I.

TABLE V. AVERAGE LENGTH OF LABOR IN HOURS

	PRIMIPARAS	MULTIPARAS	REPORT
Unmedicated	16	12	Irving <sup>17</sup>
Barbiturate-scopolamine	14.9	8.8	Rathbun <sup>15</sup>
Demerol-scopolamine	12.4	7.6	Schumann <sup>16</sup>
Apomorphine-scopolamine	11.3	6.5	present report

The distribution of cases in this study was 208 primiparas and 292 multiparas. Granted that it is difficult to determine accurately the time of onset of labor, nevertheless the comparative data charted here are arrived at the same hospital. In this institution, it is recorded as the time when uterine contractions begin to exert an effect on the cervix, either dilatation or effacement. For patients who are admitted late in the first stage of labor, the time when regular five-minute contractions began is taken as the onset of labor. The present series shows a significant reduction in average length of labor for both primiparas and multiparas.

Effect on Blood Loss

The estimated effect on blood loss in the third stage of labor in this series is charted in Table VI. Hemorrhage in the third stage of labor is influenced by many causes.

TABLE VI. ESTIMATED BLOOD LOSS

	NO. OF CASES	PERCENTAGE
Normal blood loss	463	92.6
Moderate hemorrhage	37	7.4
Severe hemorrhage	0	0

Where the total estimated blood loss was not over 200 c.c., the case came into the category of normal blood loss. In many instances in this group the estimated blood loss was 50 c.c. to 75 c.c. or less. Moderate hemorrhage was considered to exist when the estimated blood loss varied from 200 c.c. to 400 c.c. or a sudden acute loss of an amount estimated to be about 200 c.c. Most of the cases resulting in moderate hemorrhage had a definite cause e.g., lacerations or retained placenta, and only a small percentage (two cases) presented atonic uteri. All were controllable by oxytocics or indicated therapy. No undesirable effects could be correlated with the pre-medication employed in this series.

The absence of any cases of severe blood loss compares very favorably with studies reported in the literature. The following chart shows this relationship in Table VII.

TABLE VII. COMPARISON OF INCIDENCE OF SEVERE HEMORRHAGE<sup>19</sup>

AUTHOR	NUMBER OF PATIENTS	PER CENT WITH BLOOD LOSS OF 500 C.C. OR MORE
Adair et al.	51	13.7
Williams	1,000	13.0
Fortin	200	7.4
Pastore	500	6.4
Peckham and Kuder	19,200	6.14
Tucker and Benaron	14,156	4.2
Urner	7,500	3.4
Vaux and Mitchell	1,000	2.8 (inhalation)
Calkins	800	2.5
Brandt	800	1.25
Polak	2,000	0.30
Vaux and Mitchell	1,000	0.00 (cont. caudal)
Authors'	500	0.00

TABLE IV. UNDESIRABLE MATERNAL EFFECTS

	EARLY TRIALS		FINAL REGIMEN	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Vomiting (moderate)	89	24.5	32	10.7
Vomiting (excessive)	3	1.5	4	1.3
Nausea without emesis	1	0.5	1	0.3
Excitement (moderate)	37	18.5	45	15.0
Excitement (marked)	6	3.0	11	3.7

Table IV shows the incidence of the more undesirable effects occurring with the use of these premedicants.

Since the principal use of apomorphine in the past has been as an emetic, special attention in this study was paid to this undesirable complication. In a previous study using demerol-scopolamine medication,<sup>16</sup> nausea with or without emesis was reported in 25 per cent of cases. Emesis following almost any kind of medication in labor is not uncommon. It is frequently seen in the unmedicated patient particularly at the beginning of the second stage of labor. In this series moderate emesis occurred in only 10.7 per cent, under our final regimen; excessive emesis in only 1.3 per cent. Nausea without emesis occurred rarely.

Excitement occurs as a complication when scopolamine in any form or combination is employed. Barnett,<sup>5</sup> using scopolamine alone, reported an incidence of 40 per cent. In our present series this undesirable effect occurred in 18.7 per cent; of this group but 3.7 per cent of cases showed rather marked excitement. We believe that more careful use of apomorphine would have reduced this group to a negligible occurrence.

There was no undesirable persistent effect seen on maternal blood pressure, pulse, or respiration. A few patients showed tachycardia which could be attributed to a scopolamine-effect inadequately met with apomorphine. A rather marked decrease in uterine activity was rarely seen; noted in five patients. This effect presumably was due to the use of medication before labor was definitely established.

Respiration, in general, showed signs of stimulation. This effect is due to scopolamine and could be neutralized by adequate apomorphine effect limited to subemetic doses. No respiratory crises were seen in this series. No cases with circulatory collapse were observed. Twitchings or convulsions were absent in this series.

Flushing of the skin and drying of the mucous membranes and skin was seen in most patients. No concomitant temperature elevation was seen. The patients would experience a generalized numbness, and drowsiness, and when properly medicated would sleep peacefully between pains. During hard uterine contractions, the patient would turn on her side or on occasion try to sit up in bed, mumble incoherently, and might exhibit meaningless picking motions with her hands.

Our impression was that our labor room with several patients in active labor medicated by this regimen was quieter than when patients were medicated with any of the previous scopolamine combinations. It is important to emphasize that when excitement did occur, larger interval doses of apomorphine controlled this complication without allowing the desirable effects to wear off. In no instance was there any demonstrable undesirable effect on the newborn.

#### Effect on Length of Labor

It is interesting to compare the effects of these drugs on the duration of labor with previous studies at this institution. The comparative effects on labor are recorded in Table V.

In a previous study at this hospital<sup>1</sup> it was reported that in a control series without supplementary anesthesia 1.9 per cent of infants did not breathe immediately on delivery. Our present study shows an even greater improvement and this is very significant, since our cases include those receiving supplementary anesthesia.

That the nonvolatile pharmacologic agents may be potent influences affecting fetal morbidity and mortality is indicated above; compare the early period with the present, i.e., a reduction of 22 per cent "slow" babies. That definite progress has been made in the judicious use and application of premedication is unquestionable. We, therefore, contend that infant morbidity and mortality can be kept low and the mothers' comfort be given adequate consideration is not only probable but demonstrated. It should be borne in mind that factors other than premedication may operate to reduce the reflex irritability of the newborn. Exhaustion and its accompanying hypoxia or anoxia of the newborn may be due to such causes as prolapse and other dislocations of the cord, abnormal positions with possible prolapse of an extremity, or extensive premature separation, as well as other abnormalities of the uteroplacental site.

During the course of labor at least two important considerations should be constantly borne in mind; the degree and rate of progress, and evidences of either maternal or fetal exhaustion. Maternal exhaustion may become evident by the appearance of dehydration, tachycardia, restlessness, and alterations in the pattern and rhythm of uterine contractions. These findings should not be explained away on the basis of premedication. Fetal exhaustion may become evident with the appearance of hypoxia, especially change in rate or irregularity of rhythm of the fetal heart, and increased activity of the fetus in utero. The treatment of exhaustion rests principally on the judicious use of hydration, dextrose, vitamins, oxygen-enriched atmospheres, in addition to proper sedation, rather than by forced delivery. Often nothing is more dramatic than the correction of fetal hypoxia by continuous administration of adequately oxygen-enriched atmospheres to the mother.

After delivery of the fetus, its air passages are immediately drained and cleared, and continued application of oxygen-enriched air is applied until the infant breathes rhythmically and without thoracic retraction, its heart rate is well maintained, its skin pink, and its reflex irritability is normal. It goes without saying that gentleness at this stage is of prime importance.

We do not hesitate to apply fluid therapy when indicated. At the Boston Lying-in Hospital we maintain a constantly functioning blood-bank with a constantly available source of compatible bloods. Every mother is Rh typed in our antepartum clinic. When transfusion is indicated for the newborn a compatible Rh-negative donor is available; the mother does not serve as the donor.

TABLE X. CLASSIFICATION OF DELIVERIES

TYPE OF DELIVERY	NUMBER OF PATIENTS	PER CENT OF TOTAL
Multiparous normal	242	48.4
Primiparous normal	88	17.6
Multiparous low forceps	22	4.4
Primiparous low forceps	89	17.8
Multiparous breech extraction	11	2.2
Primiparous breech extraction	11	2.2
Multiparous twins	7	1.4
Primiparous twins	2	0.4
Manual or forceps rotation of head		
Primiparous	18	3.6
Multiparous	9	1.8
Hysterotomy	1	0.2



### Effect on the Newborn Infant

To evaluate the effect of the premedicants on the infants, the following classification was used:

1. Immediate spontaneous respiration.
2. Delayed spontaneous respiration, i.e., infants cried and breathed without any resuscitative measures after a delay of one or two minutes.
3. Resuscitated easily, i.e., resuscitative measures consisted of inversion of baby with rubbing or gentle spanking on back of thorax and intermittent administration of oxygen-enriched air after clearing the airway.
4. Resuscitated with difficulty, i.e., measures which included tubbing, continuous administration of oxygen-enriched air, mouth to mouth insufflation, tracheal catheterization on occasion, and the use of an analeptic, e.g., coramine, 1 to 2 c.c. given intramuscularly.

The routine procedure following delivery is to grasp the feet, hold the infant with head downward, neck extended, and thus drain and aspirate with a bulb syringe the secretions from the air passages. Gentle rubbing of the back was all that was necessary to make the infant cry in nearly all cases.

The incidence of fetal morbidity and mortality in this series is shown in Table VIII.

TABLE VIII. FETAL MORBIDITY AND MORTALITY

STATUS AT BIRTH	NUMBER OF BABIES	PER CENT DISTRIBUTION
Immediate spontaneous respiration	415	82
Delayed spontaneous respiration	58	11
Resuscitated easily	24	5
Resuscitated with difficulty	7	1
Stillbirths	5	1

In this series of 500 deliveries there were 509 births, the difference being accounted for by 9 pairs of twins, 7 pairs of twins from multiparous mothers and 2 pairs of twins of primiparous mothers. The group "immediate spontaneous respiration" corresponded to the "active" group classified by previous reports from this clinic.<sup>17</sup> The groups "delayed spontaneous respiration" and "resuscitated easily" correspond to the previous classification "slightly slow," and the "babies resuscitated with difficulty" corresponds to the "slow" group. On this basis 98 per cent of the newborns in this study were either "active" or "slightly slow," whereas but 1 per cent were either "slow" or stillborns.

That the routine use of premedication for purposes of obstetric amnesia and analgesia has actually been accompanied by a lower stillbirth and neonatal death rate at our hospital is unquestionable.<sup>17, 18</sup> We attribute this effect to a more conservative policy in the conduct of labor.

It is interesting to compare our present results with previous studies at this hospital on the effect of premedication on the newborn. This comparative effect is indicated in Table IX.

TABLE IX. EFFECT OF PREMEDICATION ON NEWBORN

PREMEDICANTS	RELATIVE PERIOD	PERCENTAGE INCIDENCE OF "SLOW" BABIES
Morphine-scopolamine	Early	23 %
Barbiturate-scopolamine	Mid	3 %
Demerol-scopolamine	Recent	3.3%
Apomorphine-scopolamine	Present	1 %

TABLE XII. PREPARTUM COMPLICATIONS (SERIES OF 500 CASES)

COMPLICATION	NUMBER OF PATIENTS
Allergy	1
Anemia	12
Asthma	1
Bronchitis	1
Cystitis	5
Diabetes mellitus	1
Epilepsy	1
Essential hypertension	1
Peripheral neuritis	1
Pyelitis	10
Syphilis	4
Tuberculosis	4
Upper respiratory infections	50
Pre-eclamptic toxemias	46

TABLE XIII. COMPLICATIONS OF LABOR IN THIS SERIES

COMPLICATION	NUMBER OF PATIENTS
Dystocia	
Cervical stenosis	1
Inertia	51
Outlet contraction	12
Rigid perineum	47
Shoulder	2
Incarcerated anterior lip of cervix	2
Malpositions	
Breech	29
Persistent occiput posterior	20
Persistent occiput transverse	10
Transverse	1
Twins	9
Occult prolapse of cord	1
Premature labor	14
Premature rupture of membranes	19
Premature separation of placenta (partial)	3
Prolapsed cord	5
Retained placenta	6
Ruptured marginal sinus of placenta	1

TABLE XIV. POSTPARTUM COMPLICATIONS

COMPLICATION	NUMBER OF PATIENTS
Aspiration of vomitus	1
Atony of uterus	2
Backache	2
Cystitis	32
Endometritis	10
Headache	11
Laryngitis with edema of uvula	1
Lymphangitis of breast	10
Phlebitis (superficial of leg)	1
Pyelitis	4
Retained lochia	1
Retained secundines	4
Retention of urine	24
Subinvolution of uterus	14
Oligogalactia	48
Fissured nipples	24

Table X is a classification of the type of delivery in this series.

Most of the multiparous normal deliveries are completed by fourth year Harvard medical students under supervision by the House Staff of the Boston Lying-in Hospital. Most primiparous normal deliveries are completed by the junior members of the House Staff. The other cases are delivered by senior House Officers under supervision of, or by members of the Resident Staff. All cases are seen by the attending staff.

It is not difficult to understand, therefore, that a variable period of time may elapse before accomplishing the delivery of the normal case. This may become a significant factor influencing the reflex irritability of the newborn, because of lack of skill and judgment in meeting the acute problem of establishing a clear airway as well as the time of exposure to anesthetic agents during delivery.

The incidence of cesarean section as reported in Table X obviously is lower than the actual incidence at this clinic. In general, scopolamine was not used extensively in patients having a test of labor, particularly following a previous cesarean section. However, this form of premedication has been used with much satisfaction in several cesarean sections subsequent to this study.

The gestational age of the patients at the time of delivery varied from 31 to 44 weeks. The distribution in this series is shown in Table XI.

TABLE XI. GESTATIONAL AGE IN WEEKS

Weeks	31	32	33	34	35	36	37	38	39	40	41	42	43
Number of Cases	1	3	3	2	3	9	9	54	65	198	88	51	14
Per cent of Total	0.2	0.6	0.6	0.4	0.6	1.8	1.8	10.8	13	39.6	17.6	10.2	2.8

About 40 per cent of the cases were delivered at term, i.e., at 40 weeks of gestation; and 91 per cent were delivered when having reached the gestational age of  $40 \pm 2$  weeks. Prematurity as well as postmaturity contribute to increased maternal reflex irritability, among other reasons because of fear for the babies' lives. By and large, no depressing effects of this drug combination were noticeable even on the premature infant. The anesthetic and obstetric risk of the mothers in this series of cases was good. In other words, by and large the patients delivered at this hospital have attended our various antepartum clinics for evaluation.

The risk of the fetus is dependent among other things on its state of maturity; age, parity, and physical status of its mother; occurrence of accidents of labor and various forms of dystocia; duration and character of labor; type of delivery; occurrence of intrauterine asphyxia; experience, skill and judgment of the obstetric team; as well as the amount and duration of pre-anesthetic depression and depth of anesthesia during delivery. Clifford and Irving,<sup>18</sup> in reporting a study at the Boston Lying-in Hospital, had shown that the type of premedicant, its dose, and time of administration have a definite relationship to prematurity and the accompanying immaturity of the fetus in their bearing on mortality and morbidity of the newborn.

In this study we found no significant correlation between the time of administration of the pre-anesthetic agents employed and fetal mortality. These observations apply also to those cases presenting prematurity in the absence of other complicating factors.

No effort was made in this study to differentiate complications as due to pre-existing condition of the patient, anesthesia, and its administration, or that due to obstetric procedures. That the postmature infant stands a greater chance

5. The ability, training, experience, attention and skill of the members of the obstetric team.

Under inhalational techniques are included open drop, semiclosed, and closed carbon-dioxide absorption, both circle filter, and to and fro (Waters) techniques. Where ether is listed in Table XV, is meant chiefly open-drop technique. By G.O.E. and/or V. are meant the nitrous oxide-oxygen-ether sequence with or without vinethene re-induction following delivery of the baby, employing the carbon-dioxide absorption closed system. The nitrous oxide-oxygen mixture at no time exceeds 50 to 60 per cent nitrous-oxide. Oxygen-enriched atmospheres are supplied during the terminal portion of the second obstetric stage, and maintained until the cord stops pulsating. The delivery is actually accomplished in the topmost portion of the first plane of the third stage of anesthesia. The accumulation of carbon dioxide in such highly oxygen-enriched atmospheres are never permitted to accumulate. The retention of carbon dioxide with its attendant disturbance in oxygen-carbon dioxide equilibrium are too well established to need further elaboration.

Under regional techniques are included spinal block and occasionally infiltration with procaine. When employing subarachnoid block, a serious attempt was made to limit the level of anesthesia to dermatomes 9 to 11. The interspace selected for injection of the agent was L4 or L3. Vasopressor substances were employed when indicated, the agent of choice was ephedrine sulfate. Incidentally, ephedrine sulfate was also used on occasion with inhalation anesthesia for its analeptic effect on the baby.<sup>10</sup>

By the group "none" in Table XV is meant the instances where delivery was accomplished without complementary or supplementary anesthetic agents. The entire delivery, including all three obstetric stages, was performed on the basis of the premedicating agents. No difficulty was encountered in this group. All the babies cried immediately on delivery. The personnel administering the anesthetics in this series of cases were of variable training, experience, skill, and judgment. The open-drop technique was employed by the nurse-anesthetists, house-officers, and some of the older members of the obstetric staff. The closed inhalation techniques were employed by the anesthesiologist member of the staff. The regional techniques were administered by the resident obstetricians or the anesthesiologist.

Table XVI is an attempt to correlate the anesthetic agent as an index of the entire anesthetic procedure with the infant's response at the time of delivery.

TABLE XVI. INFANT RESPONSE VS. ANESTHETIC AGENT

	ETHER		PROCAINE		G.O.E. AND/ OR V		PREMEDI- CANT ONLY		TOTALS	
	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT
Immediate spontaneous respiration	250	81	111	91	33	57	21	100	415	82
Delayed spontaneous respiration	31	10	7	6	20	34	0	0	58	11
Resuscitated easily	17	6	3	2	4	7	0	0	24	5
Resuscitated with difficulty	6	2	1	1	0	0	0	0	7	1
Stillborn	4	1	0	0	1	2	0	0	5	1
Totals	308		122		58		21		509	100

That the degree of narcosis and the differential anesthetic influences enumerated are potent factors affecting the irritability of the newborn is indicated in this table. When ether was employed, the depth of narcosis to which the mother was exposed usually corresponded to lower first or top second plane of third

of succumbing either before or during labor is now generally accepted as a fact.<sup>15</sup> That many factors other than premedication influence the condition of the newborn is also unquestionable.<sup>18</sup>

The maternal complications presented by this series of cases are grouped into three categories, prepartum complications, complications of labor, and postpartum complications. Their distribution and occurrence are presented in Tables XII, XIII, and XIV, respectively.

This regimen of premedication was not used in patients presenting the prepartum complication of heart disease classified as I or I-A.<sup>14</sup> The group of patients presenting the prepartum complications referable to the function of respiration, e.g., asthma, bronchitis, and upper respiratory infections, were not only improved with this group of pre-anesthetic agents, but in many instances were actually cured of their disease. However, we are not offering this regimen of medication for the patient in labor as a universal cure for upper respiratory infections.

It is interesting to observe that of the 50 cases presenting upper respiratory infection, including cough, none had their postpartum convalescence complicated by any respiratory abnormality. There was not a single instance of postpartum major respiratory complication. We think a major beneficial therapeutic effect was contributed by the scopolamine-apomorphine regimen used during labor.

The case complicated by aspiration of vomitus was a 33-year-old para iv, essential III, at thirty-seven weeks of gestation with adequate pelvis, terminating in six hours of labor by normal delivery of a 10 pound, 13 ounce baby. The placenta was delivered in twenty minutes. The emesis occurred during open drop ether induction. The patient made an uneventful recovery and was discharged with her baby well on the twelfth postpartum day. Premedication cannot wholly compensate for the deficiencies of personnel attempting to administer anesthetics.

Atony of the uterus is of great importance to both the obstetrician and anesthesiologist. Premedication and anesthesia may well be considered among the many known and unknown causative factors producing this serious complication of labor. However, in this series scopolamine-apomorphine premedication could not be assigned as an etiologic factor leading to atony of the uterus.

The anesthetic agents and techniques employed for the completion of the different types of deliveries are shown in Table XV.

TABLE XV. DISTRIBUTION OF ANESTHETIC AGENTS AND TECHNIQUES

	NUMBER OF CASES	PER CENT OF TOTAL
Inhalational techniques:		
Ether	308	61
Gas, oxygen, ether and/or vinethene	58	11
Regional techniques:		
Procaine	122	24
None	21	4

The number of cases listed refers to the newborns. Inasmuch as the pre-anesthetic agents employed are constant factors within limits,<sup>2</sup> the differential anesthetic factors influencing the newborn during completion of the delivery must be either one or more of the following:

1. The anesthetic agent.
2. The anesthetic technique.
3. The depth and duration of anesthesia required or maintained.
4. The obstetric complication presented by both mother and her fetus.

depressed states of mother and baby. To obviate these occurrences and still retain the advantages, we have employed apomorphine in subemetic doses. When used properly this pharmacologic agent has proved an invaluable aid to the armamentaria of the obstetrician aiming to accomplish safer amnesia and analgesia in labor. The regimen of medication with scopolamine-apomorphine does not appear to influence the progress of the natural forces of labor.

The properties of scopolamine and apomorphine are briefly reviewed from the obstetric point of view. Their manner and method of administration are suggested.

The effectiveness of this drug-combination compares very favorably with other methods employed by us in the past. This method may be used in conjunction with other known and accepted procedures of accomplishing obstetric amnesia and analgesia. When so used, the amounts of other premedicants as the barbiturates or demerol may preferably be decreased or eliminated.

The average primiparous labor in this series was 11.3 hours, the average multiparous labor was 6.5 hours. Apomorphine-scopolamine premedication does not appear to influence the third stage of labor; blood loss compares favorably with those reports appearing in the literature.

This combination exerts no demonstrable depressant effect on either full-term or late premature infants. It may be administered by any route. No demonstrable influence on fetal morbidity or mortality can be seen when the premedicants alone are used to complete the delivery. On the whole, this combination is better from both maternal and fetal standpoints than other methods employed at this hospital.

Scopolamine-apomorphine help to reduce the incidence of postpartum respiratory complications even in the group presenting some prepartum respiratory complication. Other complications are no greater than occur substantially in a corresponding group of nonpremedicated obstetric patients.

As shown previously,<sup>20</sup> the anesthetic agent and technique employed to complete the delivery is not as important as the ability, training, skill, attention, and experience of the person administering the anesthesia. The training and skill of the individual obstetrician may frequently be the determining factor as to the degree and duration of narcosis required to complete the delivery. Obstetric procedures that can be well and skillfully executed under top first-plane anesthesia should not have more profound narcosis. The supply of highly oxygenated atmospheres to the mother for its effects on both mother and baby is consistent with good practice of obstetric anesthesia.

There is much yet to be learned about the pharmacology of apomorphine in subemetic doses. This might prove a fruitful field of investigation for the experimental pharmacologist. Apomorphine hydrochloride in subemetic doses is a valuable addition to the clinical therapeutic agents employed by the anesthesiologist and the obstetrician.

We wish to thank Dr. Frederick C. Irving for many valuable suggestions throughout this study.

stage of Guedel's classification. When other inhalational agents were employed, the depth of anesthesia corresponded to mid or top of first plane and even on occasion to lower second stage. Whereas when procaine or no added anesthetic agent was employed, the depth of narcosis corresponded to the bottom of second stage.

The troublesome complications of headache and backache occurred much more frequently where the regional anesthetic procedures were employed. No headache or backache occurred in the group where premedicants only were used. Transient headache of no troublesome nature occurred in the inhalational group only about one-tenth as often as a complication following spinal anesthesia; headache in the postspinal group was of a troublesome character when present.

The best showing is in the group where premedicants alone were used to accomplish delivery, indicating that these pharmacologic agents are comparatively harmless to mother and infant. The stillborns in each category have an adequate explanation based on definite pathologic findings not even remotely related to the premedication or anesthetics.

When employing the inhalation anesthetic agents, slightly more agent is required for induction with this regimen of premedication as compared with the premedicants previously reported from this hospital. A basic explanation for this phenomenon is the occurrence of less depression during labor when scopolamine-apomorphine amnesia and analgesia are employed. Incidentally maintenance of anesthesia requires no more agent than that used with previous premedicants. Emergence from anesthesia is reported by most patients as pleasant or in more glowing terms.

Referring again to Table XVI, we note that immediate spontaneous respiration and immediate cry on delivery occurred in 100 per cent of the infants delivered with an effective regimen of scopolamine-apomorphine. Considering the group resuscitated with difficulty as equivalent to "slow" babies, we note that none occurred when premedicants alone or closed inhalation carbon-dioxide absorption techniques were used. On the other hand, slow babies occurred in the group where ether alone or procaine (spinal anesthesia) was used to complete the delivery. Earlier in this paper it was pointed out that factors other than anesthetic agent and technique may operate to cause depressed reflex-irritability of the newborn.

### Summary and Conclusions

Apomorphine in subemetic doses and scopolamine have been used to produce amnesia and analgesia in labor in a series of 500 patients at the Boston Lying-in Hospital. The use of a short-acting barbiturate (seconal) in limited hypnotic doses was employed early in labor before uterine contractions reached the intensity of pain to require the full regimen of medication. The object of this study was to determine the maternal and fetal effects of this combination of pharmacologic agents.

Our primary objective in medicating the obstetric patient during labor is the production of complete amnesia and a degree of analgesia that is consistent with safety for mother and baby. For the former objective we have always employed scopolamine as the amnesic drug of choice at this hospital. To potentiate its analgesic effect, various efforts have been made in the past. There are certain merits in each system. There also have occurred in the past certain undesirable side-effects, some complications of a nonpredictable nature, and uncontrollable

# SURFACE TENSION AS A FACTOR IN THE RESISTANCE OF NEONATAL LUNGS TO AERATION

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**M**OST of those who have examined the lungs of stillborn and newborn infants are impressed with the large number of cases in which amniotic fluid fills the alveoli. From this and other observations some investigators have been led to assume that aspiration of amniotic fluid occurs normally in every fetus, whereas others deny this. Since it has not as yet been possible to determine unequivocally the normal state of the lungs just before birth, we must rely for an answer on the evaluation of the circumstantial evidence.

When comparing the lungs of stillborn infants with those of newborn infants who have breathed for a few hours or days, one observes the following unexpected difference. In stillborn infants all the alveoli are usually uniformly expanded with fluid, whereas in many liveborn infants areas of complete atelectasis alternate with aerated portions for days after birth. An effort has been made to explain this difference, and its results will presently be described.

Before discussing the findings in infants with aspiration of fluid or atelectasis, brief reference should be made to the eminent importance of these conditions. Beek<sup>1</sup> found that 41.5 per cent of all neonatal deaths in his material were due to intermittent cyanosis with atelectasis. This apparently includes all fatal cases with poor aeration of the lungs, as no separate figures for aspiration of amniotic fluid are given.

As will be apparent from what follows, it is important to distinguish three conditions of the lungs of newborn infants, namely, atelectasis, aeration, and expansion with fluid. Upon gross examination at autopsy it is easy to recognize aeration. However, true atelectasis and expansion with fluid can only be distinguished from each other by microscopic examination except in cases of aspiration of extreme amounts of amniotic sac contents. This has been emphasized by Farber and Sweet.<sup>2</sup> Unfortunately, many authors have classified all nonaerated lungs as atelectatic. This is probably due to the necessity of making a provisional anatomic diagnosis at autopsy, based on the gross appearance alone. In order to avoid the unjustified diagnosis of atelectasis in these cases, we have adopted the policy at the autopsy of listing as "nonaeration" the condition of all lungs of stillborn infants and newborn infants which are not aerated or grossly filled with amniotic sac contents. The specific diagnosis of atelectasis or aspiration of amniotic fluid is only made when microscopic sections are available.

## Review of the Literature

It has been assumed that the fetus normally performs respiratory movements and aspirates amniotic fluid. A review of the older literature on this



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Windle and co-workers<sup>13-15</sup> have criticized the animal experiments of the above-mentioned authors and pointed out that such procedures as laparotomy, even without opening the uterus, may upset the oxygen supply of the fetus and stimulate respiratory movements. Their own experiments consisted of the injection of thorotrast into the amniotic cavity of guinea pigs, and subsequent x-ray examination of the fetuses in situ.<sup>13</sup> As long as there was no further interference, the fetus was apneic and did not aspirate amniotic fluid. As soon as anoxia occurred the injected material entered the lungs. The authors also mention six cases of amniography in human subjects, with no evidence of aspiration as seen by x-ray in situ. If an animal fetus was preserved in such a manner that anoxia was prevented during the experiment, its lungs were found to be atelectatic. However, if there was any delay during the manipulation, the fetus started to gasp in utero and then presented alveoli expanded with fluid, similar to those of human stillborn infants.<sup>14</sup> Other authors who have examined human newborn infants believe that true atelectasis is the normal condition of the fetal lung.<sup>16-18</sup> Windle<sup>15</sup> acknowledges that the lungs of stillborn infants show alveoli distended with fluid and explains this by terminal anoxia and consecutive pathologic aspiration. Potter<sup>19</sup> states that if the presence of fluid in the alveoli is evidence of asphyxiation, "this dissection has never seen a nonasphyxiated stillborn fetus among almost three thousand." Some authors feel that this conclusion, which is apparently not accepted by Potter herself, is correct.

Zetzelman<sup>20</sup> examined the lungs of two stillborn anencephalic monsters, and found them to be atelectatic. He assumes that this is the normal condition in utero, which was preserved in these cases because there was no intact respiratory center to respond to anoxia just before birth. However, one might object that the same defect of the respiratory center also prevented whatever respiratory movements may normally occur in the fetus, and that therefore the condition in these anencephali was not the normal one.

All observers agree that the presence of much solid or fatty material in the aspirated fluid constitutes a danger because it may obstruct air spaces or stimulate an inflammatory reaction. It is common knowledge that amniotic fluid usually does not irritate the lung tissue even if it contains cornified cells, fatty vernix or meconium. Yet, all writers<sup>21-26</sup> agree that congenital pneumonia which is relatively rare, occurs only in those lungs which contain aspirated amniotic sac contents.

The factors which may resist the aeration of an atelectatic lung after birth have been studied by Wilson and Farber,<sup>16</sup> and summarized as follows: cohesion of the moist surfaces of collapsed alveoli; imperfectly developed or injured respiratory center; an imperfectly developed thoracic mechanism; bronchial obstruction. To these factors Clifford<sup>27</sup> added another, namely, an increased turgor of the lung tissue due to congestion, edema, or hemorrhage.

### Observations

*Microscopic Examination of Lungs.*—The morphology of the lungs of stillborn and newborn infants has repeatedly been examined, and findings in the present series are not different from those previously described. A series of 30 stillborn and 30 newborn infants up to three days of age were used to outline the stages in the expansion of the lungs with fluid or air, and indicate the frequency of their occurrence. The stages in the expansion of lungs are presented in a diagram (Fig. 1). Sections of representative examples are shown in Figs. 2 to 7. The incidence of these conditions in the present series is given in Table I.

Complete or nearly complete atelectasis (Fig. 2) is sometimes seen in young infants, and rarely in stillborns. It is therefore apparently uncommon for a fetus to die without a terminal episode of anoxia with respiratory movements.

subject has been given by Farber and Sweet.<sup>2</sup> More recently several authors have supported this view and based their contention on two lines of evidence. One is the observation of animal fetuses in utero<sup>3-5</sup> and the other is the presence of amniotic fluid in the alveoli of stillborn or newborn individuals.<sup>6</sup> Some workers<sup>3, 5</sup> go so far as to assume that a rhythmic flow of amniotic fluid is essential for the normal development of the lungs. Patterson and Farr<sup>7</sup> hold that atelectasis is abnormal in the fetus, and that it is produced by solid material such as vernix, obstructing the allegedly normal flow of fluid in the bronchial tree.

As evidence for the normal occurrence of intra-uterine respiratory movements, Snyder and Rosenfeld<sup>3</sup> describe experiments in which uteri of rabbits were exposed and India ink injected into the amniotic cavities. The particles were recovered in the lungs except in those cases in which respiration was depressed by drugs. Actually this proves only the susceptibility of the fetal organism to those drugs. Potter and Bohlender<sup>8</sup> found normally developed lung tissue with fluid in the alveoli in maldeveloped fetuses in which there was no communication by which amniotic fluid could have been aspirated. They conclude that the alveolar fluid in their cases was secreted and that a tidal flow of amniotic fluid is therefore not essential for the normal development of pulmonary tissue.

Reifferscheid and Schmiemann,<sup>9</sup> and Ehrhardt<sup>10</sup> injected x-ray opaque material into the amniotic cavity of human fetuses, and followed by radiography of the fetus in utero the ingestion and aspiration of the substance. These observations were made while the fetus lived under normal conditions, as far as one can determine. Yet, the histologic sections of Reifferscheid and Schmiemann's cases show the injected material in lumina much more widely distended than is usual in the fetal lung. Ehrhardt points out that the thorotrast must be concentrated in the lungs in order to cast a shadow, because of the great dilution by amniotic fluid. This concentration is believed to be due to absorption of fluid on the lungs. Very recently, Davis and Potter<sup>11</sup> made similar experiments and injected thorotrast into the amniotic cavity of human fetuses a few hours or days before the termination of pregnancy. No roentgenograms of the fetuses in utero were made. The full-term fetuses were delivered by cesarean section. All survived, and part of them showed by x-ray thorotrast in the lungs. Younger fetuses were obtained from pregnancies terminated by hysterectomy. They were delivered by incision of the uterus in situ, and "all made repeated respiratory efforts" while they were being taken to the x-ray laboratory. Almost all of them showed thorotrast in the lungs. The authors' conclusion that the material was aspirated in utero, is however, not compelling. It is well known that amniotic sac contents are always ingested by the fetus. In these cases mouth, pharynx, and the larger air passages were filled with thorotrast as can be seen in the published roentgenograms, so that considerable amounts of this material may have been aspirated after delivery. Ligatures placed around the neck of the fetus in order to prevent such aspiration, were apparently inadequate. As the authors themselves admit, the majority of the microphotographs in their report show evidence of extraterine respiration.

Potter and Adair<sup>12</sup> assume that the fetus normally aspirates amniotic fluid, and illustrate this by a photograph of a lung section from a fetus at term (presumably stillborn) with partially expanded alveoli with fluid. On the other hand, they show a section from a liveborn infant with but a few alveoli aerated by artificial respirations, and the rest of the tissue completely atelectatic. No explanation of this difference is given. In view of similar findings to be described below, and in accord with other workers to be quoted presently, one may explain this as abnormal aspiration in the former specimen, and normal atelectasis in the latter.

TABLE I. STATE OF EXPANSION OF THE ALVEOLI IN 30 STILLBORN INFANTS AND 30 NEWBORN INFANTS UP TO 3 DAYS OF AGE

	STILLBORN	NEWBORN
Atelectasis (bronchioles filled with fluid or air)	2	8
Few alveoli expanded with air	-	6
Areas of expansion with air predominant	-	4
Mixed expansion with fluid and air	-	10
Diffuse partial expansion with fluid	17	1
Complete expansion with fluid	11	1
	30	30

fluid and with air is not great, as will be seen later in a case of mixed expansion (Fig. 7). The aspirated fluid may be clear or contain various amounts of fatty vernix, cornified cells, or bile-stained meconium. The appearance of these substances in sections of lungs has been described in detail by Farber and Sweet.<sup>2</sup>

The present observations do not support the assumption that atelectasis in the fetus is the result of obstruction of bronchi by vernix.<sup>7</sup> Atelectasis is not commonly found in those lungs which contain large amounts of aspirated solid material. Stillborn infants who often show much vernix in their lungs, do not have atelectasis as frequently as do liveborn infants who had not aspirated vernix, and die of various causes.

Aeration of atelectatic lung is preceded by the entrance of air into the bronchial tree. It is not rare to find only the bronchi and bronchioles filled with air in infants that lived for several hours, without aeration of the alveoli proper (eight cases, see Table I). In some instances further progress of aeration is prevented by previously aspirated vernix which lines the air-filled bronchioles (Fig. 3). When a predominantly atelectatic lung expands with air there is no intermediate condition in which all alveoli are partially expanded. Those alveoli which contain air are completely expanded, and are side by side with completely atelectatic ones (Fig. 6). Expansion proceeds by an increase in the number of aerated alveoli rather than a gradual increase in the volume of every alveolus, as is the case in aspiration of fluid. The probable cause of this difference is discussed in the following section.

One-third of all lungs of liveborn infants in the present series show on section no air in the alveoli, being either atelectatic or filled with fluid (Table I). Another one-third of these lungs showed full aeration of part of the alveoli, while the others are atelectatic. The remaining one-third has part of the alveoli more or less expanded with fluid and other alveoli aerated. It is obvious that in these lungs fluid was aspirated in utero but not in large amounts, so that after birth air could be aspirated in addition. Here, as in the partly aerated lungs described above, the air has accumulated in some alveoli and fills these completely, while others contain no air. If the fluid in some of the alveoli contains no solid or fatty debris, it may not show in histologic section, and be mistaken for aeration. It is then necessary to examine the alveolar walls. Aerated alveoli have straight or uniformly curved walls, whereas after aspiration of fluid the walls are somewhat wrinkled so that a cross-section appears wavy. The difference in the appearance of the alveolar walls after aspiration of fluid or air is shown in Fig. 7.

Figs. 2-7.—Sections of lungs of infants, showing various stages of aspiration of fluid or air. Hematoxylin-eosin stain (X55).

Fig. 2.—Three and one-half-hour infant. Complete atelectasis.

Fig. 3.—Ten-hour infant. Atelectasis; bronchi filled with air or fluid, and lined with vernix membranes.

Fig. 4.—Stillborn infant. All alveoli are partially expanded with fluid.

Fig. 5.—Stillborn infant. All alveoli are expanded with fluid.

Fig. 6.—Three and one-half-hour infant. A few alveoli are fully expanded with air, all others are atelectatic.

Fig. 7.—Some of the alveoli (X) are fully expanded with air; others are expanded to a less extent with fluid.

In one of the two stillborns in the present series that showed atelectasis, the aspiration of fluid was prevented by masses of thick mucus filling the large bronchi.

The manner in which a lung is expanded with fluid is different from that of expansion with air. If both occur in the same lung, it is obvious that aspiration of amniotic fluid precedes that of air. As was mentioned above, the principal argument concerns the regularity with which fluid is aspirated by the normal fetus. There is no lung in the present series in which one could be sure that no fluid had been aspirated in utero. Small amounts of fluid as they are present in every lung will not be mentioned in the following classification. This fluid is of no significance because, as Snyder and Rosenfeld<sup>6</sup> point out, the surface of the alveoli increases so much in subsequent air breathing that the amount of fluid is negligible.

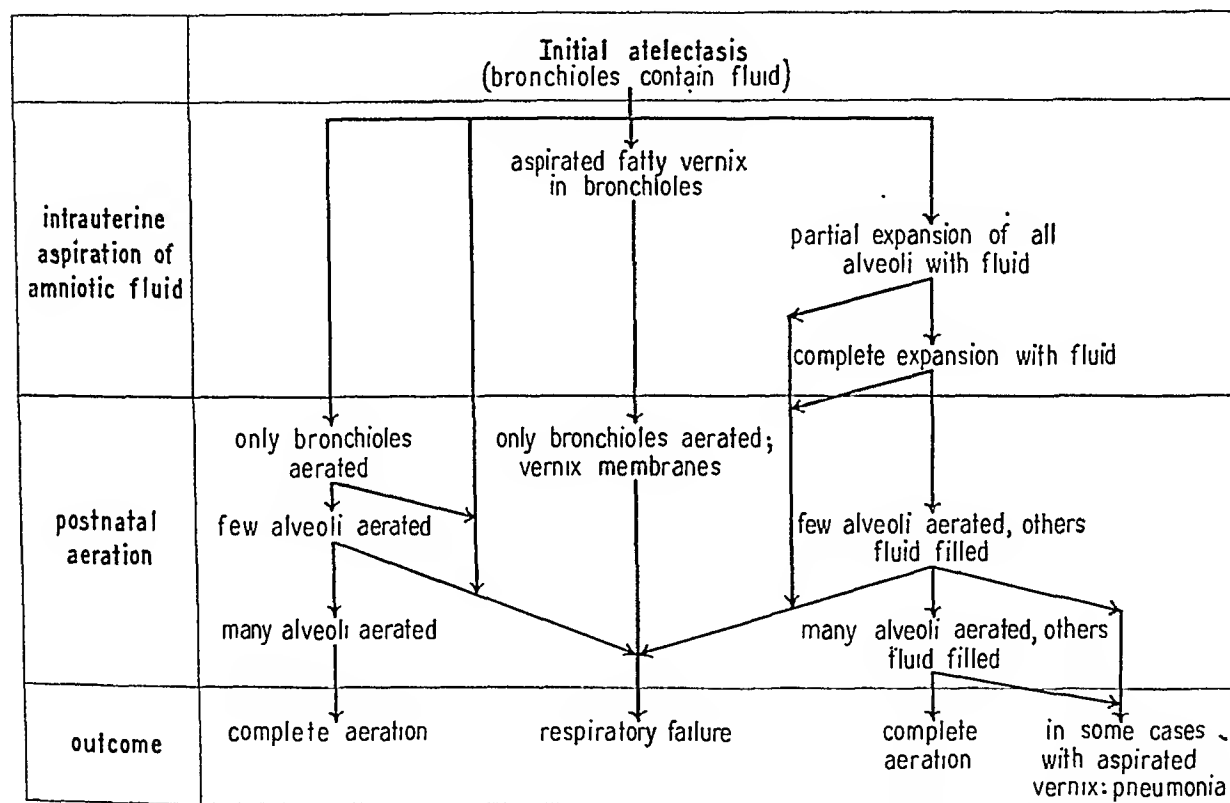


Fig. 1.—Diagram of the conditions produced in the lungs by aspiration of amniotic fluid, or air, or both.

More extensive expansion with fluid affects all alveoli almost uniformly. Thus, a lung expanded in utero goes from atelectasis to a state of diffuse partial expansion of all alveoli. All spaces are open but are flat and their walls are wavy and obviously not under tension (Fig. 4). As more fluid enters, the alveoli become polygonal with approximately equal diameters in all directions. These are referred to in Fig. 1 and Table I as complete expansion with fluid. However, it can be seen that the alveolar walls are still not completely stretched and have on section more or less wavy outlines (Fig. 5). Förster<sup>18</sup> has called attention to the fact that histologic stains for elastic fibers show wavy alveolar walls if a lung is filled with aspirated fluid, in contrast to straight walls in aerated lungs. In the present series no case was found in which the alveoli were distended with fluid to the same extent as is found in aeration. However, the difference in alveolar size between lung tissue completely expanded with

The relative amounts of aerated and fluid-filled lung tissue vary greatly in these cases of mixed expansion, and it depends on several factors whether or not adequate respiration can eventually be established. Apart from extrapulmonary conditions, one must consider not only the amount of aspirated fluid but also its nature. The infant with its low oxygen requirement may survive with partly aerated lungs until a clear fluid is absorbed. On the other hand, solid or fatty debris will remain in the alveoli and either mechanically prevent aeration or produce pneumonia, particularly when infection supervenes.

### The Mechanism of Expansion With Fluid and With Air

Several observations suggest that there is in the lung tissue a greater resistance to aeration than to expansion with fluid. It takes an infant several days of breathing to fill all or most of the alveoli with air, whereas in utero periods of anoxia which can hardly be assumed to last even as long as one hour suffice to expand all alveoli with fluid. Another finding of interest in this connection has been described in the preceding section. It was seen that a given amount of air enters the smallest possible number of alveoli and fills these completely so that apparently no additional alveoli are aerated until sufficient air is aspirated to distend the open air spaces to the limit of their normal expansion. Fluid on the other hand may partially expand alveoli to various degrees.

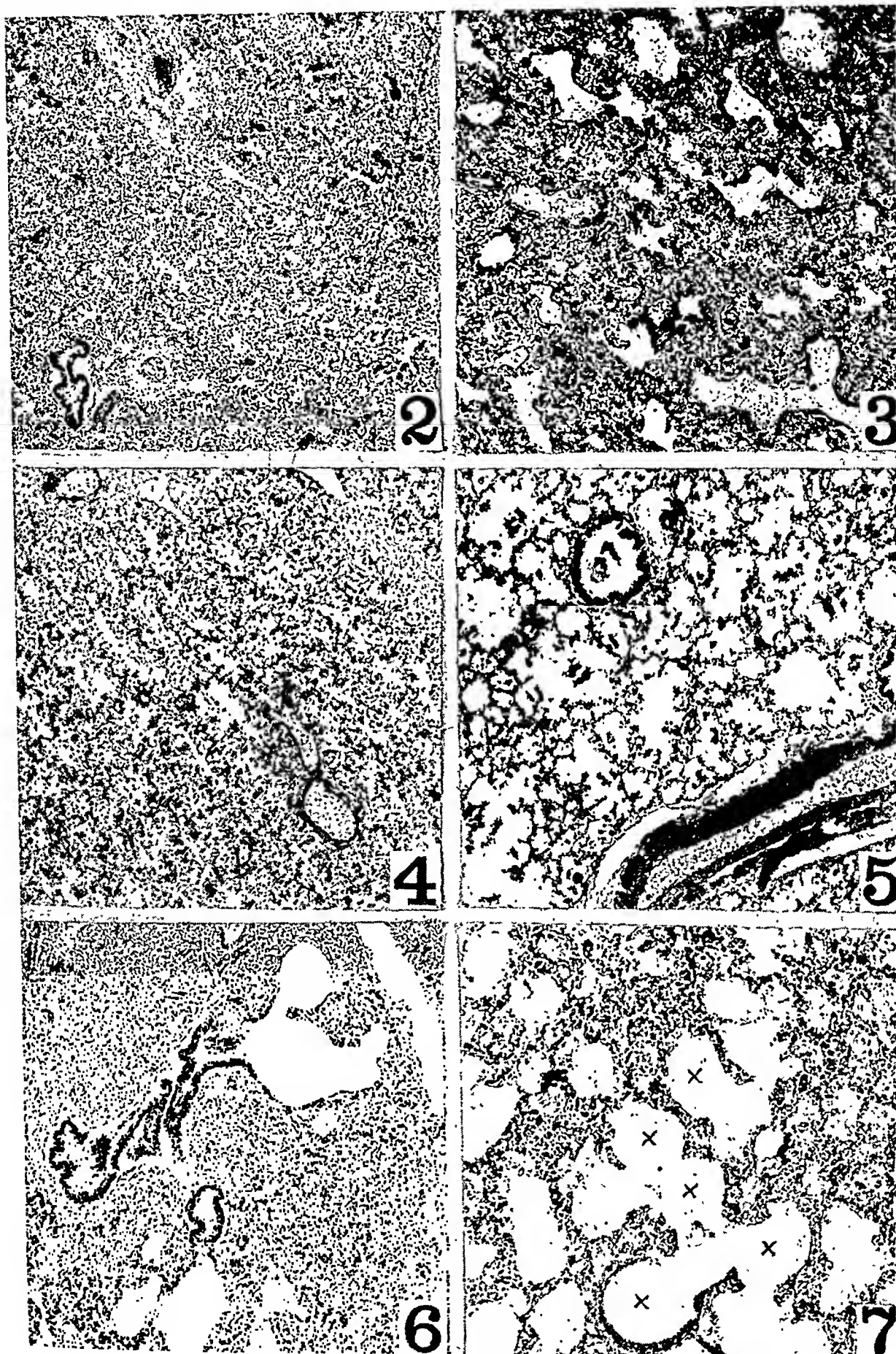
The explanation suggests itself that surface tension counteracting the establishment of the very large area of contact between a fluid surface (that is, the moist alveolar wall), and air is responsible for this difference. Whatever air enters will tend to form the largest possible accumulation and thus the smallest possible surface. When air enters the collapsed alveolus this phenomenon assumes the well-known form of adhesion of moist surfaces which has been referred to by Wilson and Farber<sup>16</sup> as one of the forces resisting aeration. On the other hand, surface tension will not resist the entrance of watery fluid into the alveoli in either large or small amounts. Similarly, if an alveolus is partly expanded with fluid, its resistance to aeration should, as far as surface tension is concerned, be just as great as if it were collapsed, because a phase boundary of the same kind must be established. It follows, therefore, that it should require much less force to expand alveoli with fluid than with air.

In order to test this hypothesis, the smallest necessary pressure was determined that is required to expand the nonaerated lungs of newborn or stillborn infants with fluid and with air. The method used is explained by a dia-

TABLE II. PRESSURE (IN CM. OF WATER) REQUIRED TO EXPAND ALVEOLI WITH SALINE OR AIR

AGE	INFANT		NUMBER OF MEASUREMENTS	AVERAGE FOR EXPANSION WITH	
	LENGTH	WEIGHT		SALINE	AIR
11 hours	38	990	2	10	24
45 min.	37.5	1120	3	12	21
24 hours	41	?	2	7	16
Stillborn	43	1820	3	3	13
Stillborn	43	2270	2	6	17
Stillborn	47.5	2220	3	5	15
Stillborn	49	2530	4	10	18
Stillborn	50	2700	2	15	21
Stillborn	50	2870	3	18	24
Stillborn	47	3110	2	9	15
Stillborn	52	3110	3	9	16
Stillborn	52	3220	2	10	18
Stillborn	50.5	3250	2	4	16
Stillborn	52.5	3700	1	11	18
Stillborn	54	3900	3	9	17
Average				9	18





Figs. 2 to 7.—(For legend see opposite page.)

TABLE III. PRESSURE (IN CM. OF WATER) REQUIRED TO EXPAND ALVEOLI, SHOWING THE EFFECT OF A SURFACE ACTIVE SUBSTANCE, AMYL ACETATE (AA). EACH HORIZONTAL LINE REPRESENTS MEASUREMENTS IN ONE LOBE, TAKEN IN THE SAME ORDER AS SHOWN (FROM LEFT TO RIGHT)

INFANT			EXPANSION WITH					
AGE	LENGTH CM.	WEIGHT GRAMS	AIR	AIR WITH AA	SALINE	AIR AFTER SALINE	SALINE WITH AA	AIR AFTER SALINE WITH AA
18 hours	40	1220	21		8			
							9	16
Stillborn	44	1650	20	15 16				
			10		5	10		
							5	8
Stillborn	46	2740	10	7				
			17		10	16		
			17				10	13
			17	14 13				
16 hours	51	2100	18		10			
			17				10	14
			17	15				
Stillborn	51	2860	13		7			
			13				7	10
			11	9				
				9				
Stillborn	54.5	4360	15		5			
			13				5	10
				10 11				

consisted in the use of air with amyl acetate vapor from a bottle similar to the lower one in Fig. 8*b*, in which the surface of the water was covered with a layer of amyl acetate. In other tests saline saturated with amyl acetate (approximately 0.25 per cent) was introduced into the lung by an arrangement similar to that shown in Fig. 8*a*. The fluid was withdrawn again as far as possible by lowering the bottle below the level of the specimen, and exerting manual pressure on the lung. Pure air was then introduced into the same lobe. These experiments were preceded by determination of the pressure values for pure saline and air. The results are given in Table III.

There was a marked reduction in the pressure necessary to introduce air when amyl acetate was used by either of the two methods. The reduction amounts to nearly one-half the difference between the values for pure saline and air. This correlates well with the reduction of surface tension by amyl acetate, as shown roughly by the height of a fluid column in a capillary (33 mm. for saline, and 21 mm. for amyl acetate solution).

Another change was noted when amyl acetate was used. The aeration was more diffuse than usual, affecting larger portions of a lobe at the same time without immediately expanding them completely. In this respect, too, the condition was intermediate between normal aeration and expansion with saline. It is thus demonstrable that surface tension is a major factor in the resistance of the lung of the newborn to aeration but does not interfere with the aspiration of fluid.

Discussion

In the lungs of newborn infants three conditions must be distinguished, namely, true atelectasis, aspiration of fluid, and aeration. The first two can



gram (Fig. 8). The fluid was 0.85 per cent saline with a small amount of India ink added so that expanded areas could be easily seen by their dark color. The fluid was introduced by means of rubber tubing and a glass cannula inserted through the main bronchus into one of its branches. The bottle with the fluid was gradually raised until the black fluid appeared in the lung tissue. The difference in level between the surface of the fluid in the bottle and the specimen was recorded. In order to introduce air another bottle was inserted as shown in Fig. 8b. Air from that bottle entered the lungs under a pressure equal to the difference between the fluid levels in the two bottles.

Only small portions of the lung were expanded for each measurement so that up to four recordings for fluid and the same number for air could be obtained in one case by inserting the cannula into several bronchi. Lungs with extensive aeration or aspiration of amniotic sac contents were not used.

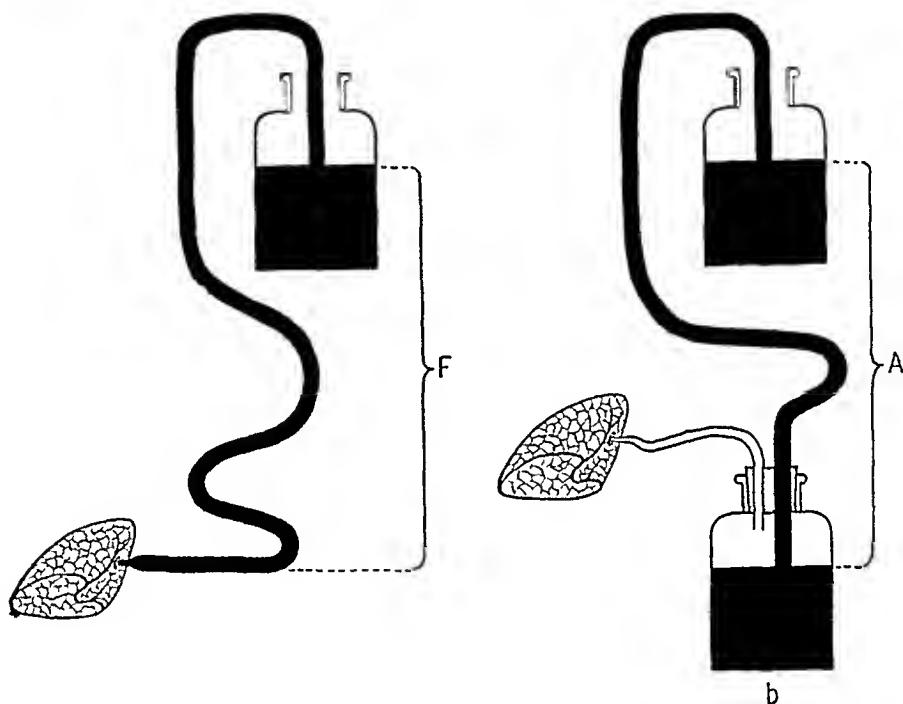


Fig. 8.—Diagram of the apparatus used for the determination of pressure necessary to inflate lungs (a) with fluid, or (b) with air. Fluid containing parts are shown solid black, air containing parts white with black outlines. (A) indicates the reading of air pressure, (F) that of pressure of fluid (both in cm. of fluid).

The results of these experiments are summarized in Table II. They show, in accordance with the hypothesis just advanced, that in every case a much greater pressure is necessary to introduce air than fluid. The average relation of pressure of fluid and air is 1:2; in the case with the smallest difference recorded it is 1:1.3; in the case with the greatest difference it is 1:4.3. All lungs were examined microscopically. As was described above, most of them had alveoli which were partially expanded with fluid, but, in accordance with the preceding discussion of surface tension, the amount of fluid present did not affect the result.

In order to demonstrate more directly the influence of surface tension on aeration, the experiment was modified in a group of six cases by the use of a surface active substance. If surface tension is the cause of the greater pressure required to fill alveoli with air, that pressure should be lowered if the tension were reduced by such a substance, e.g., amyl acetate. In the present experiments, amyl acetate was introduced into the lung by two methods. One